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THE GRASP REFLEX AND THE INSTINCTIVE GRASP REACTION[1]

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I. Introduction

The phenomena commonly comprised by the term "forced grasping and groping" are of interest to the neurologist both in the complexity of their mechanism and in their practical value as localizing signs. We are here concerned with the essential nature of the responses and will make only passing reference to the anatomical situation of the lesions which lead to their appearance.

Liepmann (1905*a*), in reporting a case of apraxia, noted that when the patient grasped an object in the left hand he was unable to relax the hand. In his later monograph on apraxia (1905*b*) he called this condition "tonic perseveration." For the next few years Rhein (1908) and others, reporting similar cases, referred to the difficulty in relaxing the grasp as "perseveration of the tonic variety described by Liepmann." In 1914, Wilson and Walshe described three further cases. Two of these showed, besides inability to relax the grasp of the affected hand, a delay in relaxation of other movements in the limb, such as extension of the elbow (their Case 1), or in lowering the raised arm (their Case 2). Their third patient, besides giving evidence of motor apraxia and persistence of a grasp once initiated, had great difficulty in using the affected limb owing to its having already grasped objects such as the bedclothes. These authors found no relationship between these phenomena and motor apraxia. They found in their three patients that the antagonists to flexors of the fingers actively contracted during the patient's ineffectual efforts to relax the grasping contraction. The defect was therefore considered to lie at a lower level of motor integration than "perseveration," which had become generally accepted as implying the undue persistence of an idea, following its use in this sense by von Sölder (1899). Wilson and Walshe therefore proposed the term "tonic innervation" for these phenomena of abnormal central persistence of a muscular contraction initiated voluntarily.

Schuster (1923, 1927) and Schuster and Pinéas (1926) re-examined the whole question. They drew attention to several additional features in patients with cerebral lesions who had difficulty in relaxation of the grasp of the hand. The movements of pursuit of an object that had touched the hand, or crossed the field of vision were described as "forced groping" (*Nachgreifen*), in distinction from the involuntary closure of the hand when an object was placed in the palm, which they called "forced grasping" (*Zwangsgreifen*). Forced grasping had, they maintained, two components. First a flexion of the fingers occurred as a result of tactile stimulus of the palm. This "schnappende Bewegung" was transient and the patient could voluntarily release the grip. Secondly there was a lasting

contraction (*Umklammerung*) which caused grasping of the object. Such lasting contraction was provoked if the object touched the palm a sufficient length of time. The strength of the grasp increased if the examiner attempted to pull his fingers from the patient's hand. Some patients had only the first phase of finger flexion but in most the lasting contraction was dominant. It was supposed that a cutaneous stimulus elicited both reactions but in one patient a lasting contraction was constantly elicited only when the examiner pulled on the patient's fingers. Both forced groping and forced grasping were independent of persistence of innervation of other joints in the limb, and were not associated with evidence of apraxia. They concluded that forced groping commonly resulted from lesions involving the frontal cerebral cortex of the opposite side, whereas forced grasping was associated with subcortical lesions and lesions involving the basal ganglia. In a later paper Schuster and Caspar (1930) studied the anatomical lesions in further patients exhibiting these phenomena and concluded that a lesion excluding the inhibiting impulses from both hemispheres was usually necessary to release forced groping completely. Lesion of the first frontal gyrus on one side and the anterior genu of the corpus callosum could be sufficient. Patients with forced grasping showed at autopsy pathological changes either in the basal ganglia or in the frontal lobe of the opposite side or in both these regions. Patients who had a lesion of the pyramidal tract in addition to a wider frontal lesion failed to develop the grasp reflex on the contralateral side but often had incomplete forced grasping and groping on the same side as the lesions.

Adie and Critchley (1927) confirmed the findings of Schuster and Pinéas in three cases of frontal lobe tumour. Forced groping was described in the following way; "Sometimes the whole arm moves so as to place the hand in the most favourable position for grasping the object that touched it. By repeating the stimulus the hand and arm can be made to move in any direction as if drawn by a magnet." They described the movements of weak flexion of fingers elicited from light contacts of the palmar surface of the thumb and forefinger. "A light stroke across the palm, preferably at the base of the fingers, causes a more active movement, often complete closure of the hand." Besides this response of finger flexion they also described a closure of the whole hand upon an object placed at rest in the open palm. They distinguished a phenomenon by which any effort of the examiner to withdraw his lightly grasped hand resulted in an increasingly powerful grasp. In agreement with Schuster these authors found no difficulty in relaxation of the empty hand. It was noted that the hand sometimes closed reflexly if an object were placed within it

during sleep and that in a patient with frontal lobe tumour the grasp reflex in the hand disappeared with the onset of severe paralysis but returned in less degree with partial return of voluntary power. The grasping phenomena were considered to be a reflex response to sensory (tactile) stimulation of the hand. Groping was evidence of disorder on a higher plane.

Walshe and Robertson (1933) reinvestigated the grasping responses and were not convinced that movements of pursuit of an object that touched the hand or entered the field of vision were at other than a volitional level. The variability in type of stimulus to evoke groping and the complex adaptation of the hand to the object to be grasped could not, they maintained, be compatible with reflex activity. The grasp response of the hand to a pull on the partly closed fingers was, on the other hand, none but a proprioceptive reflex, and as such was an aspect of "tonic innervation." The patient could relax the grasp until the pull on the flexors elicited the proprioceptive effect. Such "tonic innervation" was a constant response which was obtainable in states of semi-coma and drowsiness when all "volitional" movement had disappeared. Walshe and Hunt (1936) later reported a patient whose "volitional" grasping was abolished by novocain block of the median, ulnar and radial nerves at the wrist, unless the patient was allowed to see the contact with his hand. With such anæsthesia a pull on the fingers such as to stretch the finger flexors resulted in a contraction "wholly unimpaired in intensity." The patient had slight hypertonus in the finger flexors with brisker finger jerks than on the unaffected side. Walshe and Hunt also noted a sustained and powerful finger flexion in response to stretch in patients with spasticity of the finger flexors, without grasping movements, and distinguished this from "tonic innervation" only by the presence of "resting hypertonus." No relationship was found between "tonic innervation" and body posture in space, or head posture in relation to the trunk.

On the other hand Kennard, Viets and Fulton (1934) had found in one patient that the "grasp reflex" was more intense when the patient lay on the opposite side. Wechsler, Bieber and Balser (1936) also found in four patients that "reflex grasping" was more intense, or only present, when the patient lay on one side with the affected limb uppermost. In their first patient these authors note that a tactile stimulus elicited a transient grasp, and that a prolonged reflex was elicited only by a pull on the flexor tendons of the fingers. It was this latter response that was affected by body posture.

The grasp response in the infant has been thoroughly investigated by Halverson (1936, 1937), who also reviewed earlier observations. Halverson

differentiated a "reflex closure" of the hand in infants from a "proprioceptive response." Simple closure of the hand was a common response to a tactile stimulus in infants. A pull on the flexors of the fingers elicited the "proprioceptive response." When "reflex closure" developed into a firm grasp it was considered that when the fingers met a resisting object, a proprioceptive response was then superadded. The proprioceptive response was favoured by previous extension of the limb, but was not changed by laying the infant on one or the other side. The "closure reflex" disappeared early in development (soon after the sixteenth week) whereas the "proprioceptive" response persisted until after the sixth month, and in some instances much longer. The "closure reflex" began to weaken when voluntary grasping first developed.

Hines (1942) has studied the development and involution of the grasp response in the fœtal and infant macaque monkey. Flexion of the fœtal digits was caused by light pressure, or even point touch, applied to the "interdigital pads." The response was intensified by stretch of the flexor tendons. For the first three weeks after birth, contact with the interdigital pad appeared to be the only stimulus that initiated finger flexion. From the fourth to the seventh or eighth week finger flexion was no longer elicited by a tactile stimulus but occurred only in response to stretch of the flexor tendons.

Schuster and Pinéas (1926) described a case with a *grasp response in the foot*. Brain and Curran (1932) described a grasp reflex of the foot similar to that of the hand in almost all infants aged under a year, and in four patients with organic brain lesions. They distinguished the foot grasp reflex from the normal plantar response, because it was of tonic character and in distinction from the plantar reflex could be elicited by light pressure upon the plantar surface of the distal part of the foot, including the toes. Hines (1942) described a grasp reflex in the foot in infant monkeys elicited by the same sort of stimulation as in the upper limb.

In 1938, Goldstein described "the tonic foot response" as a slow plantar movement of the toes which persisted for some time after cessation of stimulation. This response was provoked by touch or pressure on the sole of the distal foot. Increasing stimulation, especially if painful, led to an increase of the movement. He assumed the response was of a character similar to the tonic grasping of the hand. It was also associated with frontal lobe lesions. In four of seven cases it was accompanied by reflex grasping of the fingers.

The grasp reflex has been reported in many conditions, including generalized diseases of the brain, in relation to other evidence of release

of cerebral control of motor function such as cogwheel rigidities and reflex sucking (Janischewsky, 1928; Kleist, 1927; Bender and Schilder, 1933; Joliffe and others, 1940).

These clinical observations have been extended by experimental studies of automatic grasping phenomena in monkeys and anthropoid apes. Richter and Hines (1932) showed that isolated destruction of the premotor area on one side caused forced grasping on the opposite side in Pithecus rhesus. This was persistent only after bilateral lesions. This observation was confirmed by Fulton, Jacobsen and Kennard (1932), and by Kennard and Fulton (1933) who summarized the result of further experimental investigations of grasping and spasticity as follows: "These signs are present for a longer period after *bilateral* than after *unilateral* lesions of area 6. In all cases of a removal of a *second* motor or a premotor area, the existence of bilateral innervation has been demonstrated by augmentation of the grasping symptoms in the ipsilateral extremities." "In monkeys and baboons, complete bilateral extirpation of areas 4 and 6 is followed by permanent and complete loss of voluntary power. Forced grasping and spasticity are extreme, and the involuntary postural and righting reflexes of Magnus and de Kleyn may be demonstrated readily. The bodily reflex status of such animals appears to be identical with that of thalamic preparations."

In 1934 Fulton called the involuntary grasping and the associated reactions following lesions restricted to the premotor area "forced grasping" which was defined as a complex grasping reaction subject to cortical modification from visual, tactile, and proprioceptive channels. The grasp reflex was defined as slow flexion of the digits in response to gentle contact with certain parts of the palmar or plantar skin after bilateral area 4 and 6 excisions, or in the thalamic animal. Stroking the skin over the metacarpophalangeal joints was an adequate stimulus in some instances. A gentle contact with the digits, so as to stretch the flexor tendons slightly, was sufficient to excite grasping but was still effecive after nerve block at the wrist. It was concluded that it could be shown readily in animals that cutaneous stimulation was "not essential for the response," but that cutaneous sensation normally cooperated with the proprioceptive stimulus as in the supporting reaction of Magnus. Indeed, in one such preparation it was found that grasping occurred in the completely deafferented limb when the animal as a whole was moved rapidly through space. Both forced grasping and the grasp reflex were found to be affected by the position of the body in space. It was further concluded that the grasp reflex is the basis of forced grasping, and is a subcortical reaction which forms part of the righting reflex mechanism of primates. Fulton regarded

groping as a cortical reaction arising chiefly from visual stimuli. In the animal after premotor frontal ablation it was stated to cease entirely when vision was abolished.

Bieber and Fulton (1938) further elaborated these studies of the grasping of the thalamic animal, which was found to show a pattern of righting reflex, of which the grasp reflex was thought to be a part. The experiments on deafferentation were again discussed and it was concluded that stretch of the digital tendons was the effective stimulus for the grasp reflex. From the experimental point of view it was considered that the "grasp reflex is the basic subcortical prehension pattern on which the forced grasping phenomenon is built." It is stated that "forced grasping" differed from the grasp reflex in being more liable to fluctuation, and in being independent of lesion of the pyramidal tract.

Hines (1942) differentiated reaching and orientation of the grasping extremity by the righting reflexes in the infant monkey from reaching and grasping movements towards objects in the field of vision. This author found that the grasp reflex differed from both these responses. This grasp reflex reappeared in the adult monkey following bilateral ablation of area 6. After bilateral ablation of areas 4 and 6 in the adult, the animal "does not flex the fingers to pressure or touch on any surface of the hand, but only to stretch on a partial chance contraction of the flexors." It was noted that following complete frontal lobe extirpations monkeys groped for objects only during change in position from either the upright or supine.

From this brief review it may be concluded that not only is there lack of precise definition as to what types of grasping should be included under the terms "grasp reflex" and "forced grasping" but the relationship of such phenomena as are described to other types of disorder of movement is confused and controversial. Wilson and Walshe (1914) originally defined "tonic innervation" as a symptom "evident solely and exclusively during voluntary innervation of the muscular groups concerned." They go on to say "the patient is unable to inhibit an innervation which he has correctly initiated," and that "with automatic movements the phenomenon is not observed." This view is difficult to reconcile with the application of the term "tonic innervation" by Walshe and his associates to a response to local muscular stretching appearing also in unconscious patients. Such use leaves unexplained and unclassified the interesting phenomena of inability to extend the voluntarily flexed elbow, or to lower the raised arm, which Wilson and Walshe (1914) expressly differentiated from apraxia and perseveration. This use of the term tonic innervation leaves unexplained the delay in opening the closed eyelids, the difficulty in opening the jaw

(Janischewsky 1928, Freeman and Crosby 1929) and the catatonic attitudes observed in many of these patients which cannot be explained by response to local stretch of muscles. Even if it be supposed that the long delay in opening the clenched but empty hand reported in one of Wilson and Walshe's cases was related to coincident accidental stimulation of his palm by the patient's own fingers, it is difficult to allow that he could stretch the flexor tendons in this way. Whereas these authors established for the first time a proprioceptive factor in the grasp reflex, this was not differentiated from spasticity, by them or by others since. The facile grasping response to a light contact with the skin of the palm so clearly described by Schuster, and commonly observed in the clinic, is, together with the great difficulty in its relaxation, not easily set aside as a perversity of "volition." Nor is it explained why such volition does not affect the opposite unaffected hand.

II. The Present Investigation

As a result of prolonged observation of a patient in whom a stereotyped variety of involuntary grasping was the leading symptom we were first greatly impressed by the part played by proprioceptive stimuli in obtaining a response. Closer investigation revealed, however, that a particular combination of cutaneous and proprioceptive stimulation was necessary to evoke it. Investigation of other patients by the same methods then revealed that our first case had presented in almost isolated form the type of grasping to which we propose to limit the term "grasp reflex." In most other patients this response was accompanied by a different type of grasping which we shall call "the instinctive grasp reaction." Indeed in some patients exhibiting the phenomena called "forced grasping" the grasp reflex may not be present though other grasping phenomena may be highly developed.

Our description begins with the isolation of "*the grasp reflex*" as a flexion-adduction response in one or more digits, provoked by a distally moving pressure contact on a particular area of the palmar aspect of the hand. The motor response thus originated is maintained by a pull on the contracting muscles. For the convenience of the reader it should here be stated that the grasp reflex, as thus defined, appears to have been termed "forced grasping" ("Zwangsgriefen") by Schuster (1923), Schuster and Pinéas (1926), and Adie and Critchley (1927), as "tonic innervation" by Wilson and Walshe (1914), Walshe and Robertson (1933), Walshe and Hunt (1936), as the "palmar reflex" by Riddoch and Brain (1923), and appears to correspond with the "proprioceptive grasp" of Halverson (1937) in infants, and probably the "flexion to stretch" of Hines (1942) in the infant

macaque. We do not believe it is wholly applicable to the various kinds of grasping described as the grasp reflex by Fulton and his associates in monkeys deprived of areas 4 and 6 and in thalamic preparations. We may also here anticipate our argument by noting that the grasp reflex is sharply distinguished by us from "*the instinctive grasp reaction*," which is a slower reaction to light stationary touch on the skin of any part of the hand. The hand is then first brought into a position appropriate for a total grasp before gripping, and the response is less stereotyped than is that of the grasp reflex. The essential difference from the grasp reflex is an "adjustment" of the hand as a whole to contain the object.

Our use of the term "instinctive grasp reaction" covers phenomena included under "forced grasping" by Schuster (1923), Schuster and Pinéas (1926), and Adie and Critchley (1927), the "volitional component" of Walshe and Robertson (1933), and Walshe and Hunt (1936). It appears to correspond with the "réflexe de préhension" of Janischewsky (1914) and the "closure reaction" in infants of Halverson (1937). It includes groping, the "forced groping" ("Nachgriefen") of Schuster (1923) and others. Under the inclusive term "the instinctive grasp reaction" we have distinguished, for descriptive purposes, five sub-varieties of reaction, namely, "the closing reaction," "the final grip," "the magnet reaction," "instinctive groping," and the "trap reaction."

Since we are not here concerned with the exact anatomy of the lesions giving rise to the phenomena under discussion the differential diagnosis and exact anatomical diagnosis of the cases cited has been reduced to a bare minimum. In all, 68 cases exhibiting the grasp reflex were studied, and these included 16 cases of cerebral tumour, 7 cases of traumatic cerebral lesion, 17 cases of cerebrovascular disease, 7 cases of intoxication (CO poisoning, &c.), 9 cases of cortical atrophy, 6 cases of diseases of the basal ganglia, and 6 cases of chronic inflammatory cerebral disease of various kinds. We studied 19 cases presenting the instinctive grasp reaction, including 3 suffering from cerebral tumour, 3 cerebral trauma, 7 cerebrovascular disease, 1 case of intoxication, 3 from cortical atrophy, 1 from a parkinsonian syndrome and 1 from chronic inflammatory cerebral disease.

III. The Grasp Reflex

(i) *The Effect of Localized Stimulation in a Typical Case.*

The following case was intensively studied because there was a well developed unilateral grasp reflex in a mentally normal person without paresis:

Case 1.—A. B. was a 53-year-old man who in the previous two and a half months had three periods of weakness of the left arm and leg, associated with headaches and tinnitus. Each episode lasted several hours. There was urinary incontinence

twice with these attacks and he was told that he slurred his speech at one time. His most recent episode was associated with severe mental confusion. All symptoms had markedly ameliorated since his last attack but he still complained of slowness and awkwardness of the left arm and hand at the time of our examination.

His past history revealed nothing of special interest. One brother suffers from chronic parkinsonism associated with reflex grasping and sucking, and another brother was reported to be suffering from paralysis following a "stroke." There was no cardiac disorder and blood pressure was 140/80 mm.

Neurological examination revealed a slightly anxious but otherwise normal mental state. There was a slight plastic type of rigidity in the left arm, some slowing of speech, and a fixity of facial expression. There was no tremor, and the tendon reflexes and abdominal reflexes were present and equal. The plantar responses were both flexor. There was no sensory loss and no distinct paresis. The condition offered some difficulty in diagnosis, for the rigidity was minimal in degree, whereas difficulty in relaxng the grasp reflex formed a major disability. An air encephalogram revealed no significant abnormality. The EEG was within normal limits. Lumbar puncture showed a spinal fluid pressure of 90 mm., with no cells, total protein, 20 mgm. and negative Hinton and Wassermann tests. Diagnosis: An unusual type of familial cerebral degeneration (? Alzheimer's presenile dementia, ? Jakob-Creutzfeld syndrome) was probably present, though cerebral thrombosis could not be excluded.

Abnormal reflex responses: The grasp reflex was elicited with ease in the left hand, not in the right. Meyer's reflex was strongly developed in the left hand, with at times a trace of response on the right. Hoffmann's sign was not elicitable in either hand. No sucking reflex was present. A grasping of the toes was present in the left foot on some days, no response on others.

Passive movement in the elbow and wrist:—right side: The resistance characteristic of normal persons who cannot relax very well. *Left side:* distinct resistance of a soft type, softening a little at the end of passive flexion and extension. It was present in both flexor and extensor groups. The resistance very markedly varied in strength and sometimes was almost zero.

Voluntary movement: Motor power in the left arm was a little less than on the right, but there was no distinct paresis. There was no retardation when opening and closing his hand to order, but active extension and flexion of the elbow was a little slower on the left side.

Gait: There was lack of the normal associated movements on the left side. The patient explained that when walking he always had to concentrate upon not gripping his coat, and he therefore tended to hold his fingers stiff all the time.

Course: During the first weeks of his hospitalization it frequently happened that the left hand clung to a door handle or other object with such tenacity that he had to use his right hand to help free himself. In the last weeks of admission all his symptoms progressively decreased and the grasping response gradually became more difficult to elicit.

The *grasping response* was examined on very many occasions and in the first three weeks of admission was as follows: If two of the examiner's fingers were laid gently across the palm of the open hand of the patient and then kept still there was usually no response. On exceptional occasions a light palpating movement of the fingers began. At first we thought these rare movements were due to some lack of cooperation but later we learned to recognize them as fragments of what we shall call the instinctive grasp response. At all other times a stationary contact whether made with soft or hard, large or small object was without effect.

If the observer's fingers were pulled out of the hand between the patient's thumb and first finger these two digits approximated, without flexion of either, so

that the examiner's fingers were compressed. If the whole of the examiner's hand were used as stimulus the thumb and index finger, and perhaps the other fingers, flexed so as to grip the escaping stimulus. A small object used as stimulus evoked a slight and often ineffective adduction of the thumb only as it passed out of the hand. In each case, if the stimulating object was grasped at all the further pull immediately intensified the reaction.

When the stimulus was introduced into the patient's hand so as to make contact with the palm and the palmar surface of his fingers, but not to touch the thenar eminence or the first digital interspace no reaction occurred. But if the stimulating object were now drawn distally over the palmar surface of the fingers the fingers flexed and if traction were made on them a strong resistance was encountered. In this reaction the thumb did not participate except that it flexed late in the development of strong resistance to traction on the flexed fingers.

If the fingers of the patient were grasped firmly they could be passively flexed and extended, rapidly or slowly, without any trace of resistance. It was clear that in the phenomenon of the grasp reflex the fingers adducted or flexed to engage or meet the stimulus and so initiate the grasping movement.

Since it was evident that the grasping response could be modified considerably by varying the region stimulated we proceeded first to investigate the effect of very localized stimulation systematically and the following scheme will serve as a pattern for all patients studied. The patient was blindfolded, and seated comfortably in a chair. Unless otherwise stated the observer's finger was the stimulating object. The response to moving light touch, and to moving pressure was examined separately, but the last was always the most effective.

The result of a localized moving contact stimulus to different parts of the patient's hand.—(1) Between thenar and hypothenar eminence near the wrist with movement toward the palm of the hand (fig. 1 at A): The reaction to a brief stimulus was a flexion of the wrist which increased in intensity as the flexion opposed the stimulus. With further increase in stimulation when the flexion of the patient's wrist was resisted by a pressure there resulted a strong flexion of the wrist, flexion of the elbow, and weak flexion of the metacarpophalangeal joint. These movements were further increased if the stimulus was intermittently intensified. If the movement was away from the palm (fig. 1 at B): *No response.*

(2) Stimulation beginning in the middle of the palm, moving toward the space between the thumb and index finger (fig. 1 at C): *No response.* If moving either medially or proximally for 2 to 3 cm. (fig. 1 at D): *No response.*

(3) Stimulation beginning in the interspace between any two digits, moving toward the palm (fig. 1 at E): *No response.* If moving distally and dorsally from the interspace (F) an approximation of the two neighbouring digits resulted. This adduction resulted in the same manner from stimulation of the web between thumb and forefinger at F'. No response occurred if the stimulus moved toward the palm (fig. 1 at E').

(4) Stimulation of the skin over the palmar aspect of any one of the metacarpophalangeal joints, moving toward the palm (fig. 1 at G): *No response.* If moving away from the palm of the hand (fig. 1 at H): there was strong flexion of each of the metacarpophalangeal joints, weakest in the thumb.

(5) Stimulation over the proximal interphalangeal joint of any finger moving toward the palm (fig. 1 at I): *No response.* If moving distally (fig. 1 at J) there was strong flexion of this joint of the digit concerned, with flexion of the neighbouring joints.

(6) Stimulation over the distal interphalangeal joints moving toward the palm (fig. 1 at K): *No response.* If moving distally (fig. 1 at L): strong flexion occurred in these joints of the digit concerned.

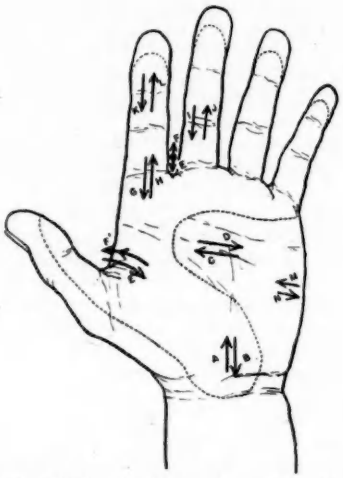

FIG. 1.—Diagram of the left hand of Case 1 to show the regions of stimulation mentioned in the text. The arrows G, H over the second metacarpo-phalangeal joint indicate only the situation of the stimulus relative to that joint, and serve as type for the 1st, 3rd, 4th and 5th joints. Similarly the stimuli I, J, and K, L, serve as type for all first and second interphalangeal joints respectively and the stimuli E, F, for skin bordering any interspace. The broken line encloses the area within which the "catching phase" of the grasp reflex could be elicited.

(7) Stimulation of the middle of the hypothenar eminence moving toward the centre of the palm (fig. 1 at M): *No response.* If moving medially (fig. 1 at N): *No response.*

(8) The combination of any two or more of the effective modes of stimulation mentioned above evoked a combination of local reactions.

(9) Eliciting any one effective local reaction made it easier to elicit any of the others (reinforcement) within the next few seconds.

(10) If the examiner's finger continued the stimulation so as to meet and oppose the movement that was elicited, a powerful reinforcement of the movement, and its spread to include flexion and adduction of neighbouring joints, occurred.

(ii) The Localized Components of the Grasp Response in Other Cases.

The systematic investigation of our first patient was repeated in the remainder of our clinical material, and will be summarized with further discussion of the various methods of stimulation that were used. The grasp reflex was elicited in 68 patients. Some of the patients were followed over a period of several weeks.

In the clinic the grasp reflex is usually elicited, following Schuster and others, by the observer's placing two or three of his fingers between the thumb and first finger of the patient's hand and withdrawing them, at the same time stimulating the thenar eminence and palm by moving contact

(a combination of touch and pressure). This method provoked a grasp reflex in 27 of our cases, and in the following account these patients are said to have a *strong* grasp reflex. In 41 patients a more effective method of stimulation, described later, was necessary to get a grasp reflex.

Since the patient can usually influence the response in some degree it is necessary to distract his attention by talking with him, or asking him to watch some object in the room, or by having him firmly close his eyes. It is not sufficient to instruct him to relax for in some it is then not possible to elicit reflex grasping though it may be easily provoked when the attention of the same patient is distracted. These precautions are as necessary for the partial response described below as for the complete reaction. The following analysis is based on the results of various modes of stimulation in the 27 patients with a strong grasp reflex.

(1) A local stationary pin-prick, touch or pressure, in any place in the palm or the palmar side of the fingers usually did not provoke any response. A distally moving touch usually provoked a movement of flexion in the neighbouring joint. A dragged pin-point evoked either simple withdrawal or a conflict between flexion of the fingers and avoiding movement, depending on the degree of noxious pressure exerted by the pin and on the facility of the reflex.

(2) Stimulation of the skin covering the hypothenar eminence or the middle of the palm, or of the palmar surface of the terminal phalanges, usually did not provoke any reaction. Only when the stimulating object was moved distally out of the palm or over the wrist, in the area enclosed by broken line in figure 1, did a contraction occur. Movement in the opposite direction, even in this area, was ineffective.

(3) A moving heavy touch over the palmar surface of a finger-joint produced a transient flexion in that joint, with a weaker flexion in the neighbouring joints of the same finger. For this to be seen clearly the stimulating object had to be withdrawn immediately the flexion developed. The stimulus was more effective when some pressure was exerted on the skin by the stimulating object. Whether the stimulating object was soft or hard, smooth or angular, made no observable difference, provided it was not nocuous.

If the grasp reflex was strongly developed, the patient's finger flexed as soon as the distally moving cutaneous stimulus reached the metacarpophalangeal joint. More often flexion did not occur before the proximal (and in some cases distal) interphalangeal joints were reached. If the reflex reaction was not too weak, the patient's finger contracted to meet the distally moving stimulus, as in figures 2A, 2B and 2C. The contraction increased suddenly in strength and persisted longer when the observer tried

to overcome the flexion response by counter-pressure on the flexing finger, then pulling the tendons of the contracting muscles. The observer had the impression that "the fish had been hooked." This reaction was easier to provoke when the examiner, as soon as he felt the first contraction of the patient's finger, increased the pressure and speed of stimulation. If the initial response was not opposed in this way the active flexion movement lasted only as long as the stimulating object was kept moving in the sensitive area.

(4) Stimulation of the "heel" of the hand between thenar and hypothenar eminences elicited a reaction usually only when the stimulating object was moved distally towards the palm. This reaction consisted of a flexion of the wrist. It was observed only in patients where the grasp reactions as a whole were very strongly developed. Flexion of the wrist increased when the observer not only touched the skin, but also pressed between thenar and hypothenar eminences, and in that way opposed the flexion response elicited by moving contact. A flexion of elbow was often seen when this flexion of the wrist was fully developed, but faded relatively rapidly if the pressure was consistently maintained. A further increase of flexion of the wrist and elbow occurred if the observer repeatedly increased passive pressure against the heel of the hand.

(5) Stimulation of the skin between any two digits by an object that was drawn fairly rapidly ventro-dorsally through the interspace between the bases of the fingers, resulted in an approximation of the two digits concerned. Such a stimulus was often more effective when repeated. If the object (pencil, examiner's finger) was drawn from the dorsal aspect into the palm it was usually ineffective. The only difference between the four interspaces was that the response from that between the thumb and first finger was often stronger than from any of the other three. The adduction of the two fingers resisted the passage of the stimulating object and if traction was then continued the adduction suddenly increased in strength. This reaction, comparable to the reinforcement of the local flexion when pulling on a flexing finger, was however never as strongly developed as flexion of the fingers or wrist.

From these findings we may conclude that when a strong grasp reflex was present, a brief isolated flexion response of separate finger-joints or of the wrist could be elicited by a distally moving contact over an appropriate area of the palmar aspect of the skin of the fingers or the palm of the hand. These responses had each the property of sudden increase in strength and of irradiation to neighbouring joints when the contraction was counteracted, and were then as difficult for the patient to relax volun-

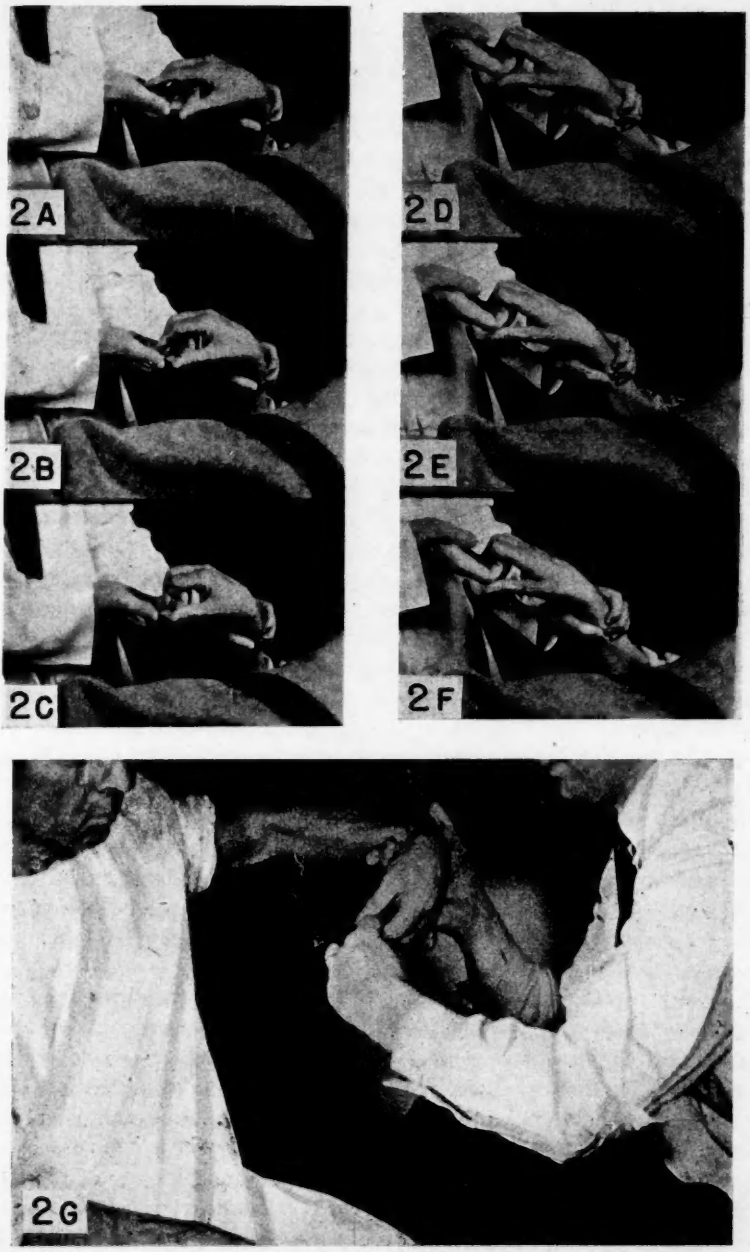

FIG. 2.—Two series of three cinematographic pictures from an examination of Case 6 to show the elicitation of the grasp reflex. The series 2A, 2B, 2C, at intervals of 1/16 second which show the "catching phase," were followed by 2D, 2E, and 2F, after an interval of 40 frames (2·5 sec.) and show the full development of the reflex. Fig. 2G (Case 1) shows elicitation of a grasp reflex in Case 1 in spite of concurrent strong passive flexion of the wrist.

tarily as was the total grasp response. The reactions of the digits and wrist may each be regarded as consisting of two phases:

(*a*) A brief, weak contraction of flexor or adductor muscles of the fingers or wrist was the first reaction of the moving touch, or touch plus pressure on the skin. We shall call this the "catching phase." The flexion movement of the fingers could be clearly seen in cinematographic analysis (figs. 2A, 2B and 2C).

(*b*) A rapid increase of the strength of the contraction when pressing (the wrist) or pulling (the fingers) counter to the elicited movement. This may be called the locking or "holding phase." Besides the pressure on the skin, the stimulus in this second phase also consists of a pull on the contracting muscles (figs. 2D, 2E, 2F). Both phases could be developed in paralytic arms when no voluntary movement was possible (2 cases).

Thus a localized stimulus may elicit a catching phase localized to one finger-joint and this is intensified in the holding phase but is still relatively localized. Once elicited the holding phase may be strong in patients in whom the initiating grasping phase is difficult to elicit. We concluded that each local reaction is a simple movement. It has a specific mode of stimulus, a definite and constant receptive field, and a regular, co-ordinated and uniform motor response. It thus may be regarded as a simple reflex.

(*iii*) *The Relation between the Local Reaction and Complete Grasp Reflex.*

When the local reaction increased in strength it also increased in distribution, including contraction of one or more of the other fingers. In patients whose grasp reflex was strongly developed, it was often possible to provoke a flexion of all the other fingers and thumb by stimulating the region of one single finger-joint. As long as only local stimulation was used a complete grasp with true opposition of the thumb to the other fingers did not usually develop.

When two of the local reactions were provoked at the same time, they reinforced each other. Thus for example, when a finger-joint reflex was developed, an associated contact with the skin between two fingers was more effective than when such a contact was made alone. For the same reason, the whole grasp was easier to elicit when using a large object, for example, the whole hand compared with a pencil. To provoke a complete grasp it was necessary to stimulate more than one of the local reactions, including those of the thumb. In the classical method of eliciting this reflex by drawing two fingers from the palm out between the index finger and the thumb, eventually five local reflexes are provoked: Adduction of the two digits due to the stimulation of the skin between their bases (1), flexion of the digits as a response to the stimula-

tion in the region of the two metacarpophalangeal joints (2 and 3) and the two neighbouring interphalangeal joints (4 and 5). The fusion of motor responses is the more complex as more local reactions were added. In the metacarpophalangeal joint there was not only a flexion or adduction, but a combination of these two movements, which in the thumb resulted in opposition. Thus that combination of flexion, adduction and opposition between the thumb and the other fingers which is usually conveyed by the term "grasping," developed from the summation of local reactions.

A full and complete grasp reflex, including the grip between the thumb and the other fingers, is not one reflex, but, when fully developed, a summation of the simple local reactions on stimulating different places of the palm and fingers. Thus different local reactions accounted for the variation of the grasping movement to suit the stimulating object.

Any form of stimulus for reflex grasping was usually more effective when repeated two or three times, indicating some summation in time. On the other hand, the strength of the reaction often declined after the first four to eight repetitions in rapid succession. In two patients, described later without power of voluntary movement in the affected limb, the first response was the most complete in each series. When the reaction was fatigued through too rapid repetition a better response could be obtained by changing the type of stimulation. This fatigability was the same for each local reaction as for the whole.

In 41 patients, especially those with cerebral atrophy, a moving light touch had very little effect, whereas heavier and more rapid pressure of the finger tips into the palmar aspect of the patient's finger followed by traction caused a strong finger flexion. This pressure had to be in a distal direction so as to stretch the subcutaneous tissues of the fingers at the same time. In most of these patients it is however necessary to stimulate more than one finger at the same time, probably indicating a high threshold for the response.

In securing preliminary relaxation and distraction of the patient the *optimum method for eliciting the response was as follows*: the patient was instructed to hold out the arm so that his unsupported hand had the palm facing downwards. With the patient's hand held thus, free in space, the inhibiting effect of pressure on the dorsum (discussed later) was avoided. If the patient's fingers were relaxed they were slightly flexed before stimulation and this posture provided the optimum condition for eliciting the response. The examiner then placed his hand under that of the patient's so as to support it and, with fingers slightly flexed, made a firm stroke from the palm of the patient's hand toward the palmar aspect of the patient's finger tips (figs. 2A and 2B). The stimulating move-

ment was made at first slowly and with firm pressure upwards into the patient's palm. As soon as the examiner felt a little flexion in the patient's fingers he moved his hand faster, in this way provoking a rapid increase in the strength of the response. This reinforcement appeared to be related to additional stretch of the already contracting flexor muscles. In the patients with little sensitivity to skin stimuli the examiner often had to pull rapidly from the start and exert a firm pressure at the same time. If there was no flexion of the patient's fingers in response to this method of stimulation, other forms of stimulation were normally useless, and the patient had no grasp reflex. Only in cases with strongly developed isolated finger responses could a grasp be provoked by drawing two fingers from the palm out between the index finger and the thumb.

Change in position of the body to the right or the left side had no influence on the strength or the irritability of the reflex in any of the cases observed. We shall refer later to certain patients exhibiting the Magnus-de Kleyn reflexes without the grasp reflex.

The influence of sleep on the grasp inflex was examined, both in infants and in adult patients. In infants the strength of the reflex was distinctly diminished in sleep but not lost. In 13 adult patients, 4 showed some decrease in the reflex during deep sleep, 9 had no change in the reflex. Only one of these patients was mentally completely normal when awake. We found that the grasp reflex could be very strong in patients so deeply semi-comatose that it could not be decided if they slept or not.

(*iv*) *The Adequate Stimulus for the Grasp Reflex.*

We have described the fragmentation of a type of stereotyped grasping response by limitation of the area of stimulation. It is now necessary to examine more closely the kind of stimulation that is adequate for the stereotyped, fragmented (or grasp reflex) response.

In cases of strong grasp reflex the importance of subcutaneous stimulation could be demonstrated by covering the palm with a piece of cloth before stimulating. The reflex then did not develop unless the observer pressed very firmly against the fingers of the patient, though the passive pull on the tendons remained the same.

In Case 1 the skin and subcutaneous tissues of the third finger of the left hand were anæsthetized on three different occasions by infiltration of the base of the finger as well as the digital nerves with novocain (1 per cent). Only in the last of the three experiments, where the insertion of the flexor digitorum profundus was also infiltrated was sense of movement and of position in the interphalangeal joints completely lost. In this last experiment no response developed in the interphalangeal joints

of the anæsthetized finger to moving touch or pressure against the skin, or to passive extension of the fingers, or even when the patient was allowed to watch the examination. The finger still flexed as part of the second phase of a general grasp provoked by stimulation of the rest of the hand, and passive stretch of this finger alone then could prolong the response in it and other fingers. If the anæsthetized finger did not flex as part of a grasp reflex, a pull on it was ineffective. This finding was confirmed also in Case 2.

Case 2.—S. S., a 65-year-old woman suffering from an extensive frontal lobe astrocytoma, had previously had a complete left sided hemiplegia following a status epilepticus with continued left sided twitching of muscles. The right side was normal by the usual neurological examination, but revealed a grasp reflex of moderate degree. Following a period of two and a half weeks of flaccid left hemiplegia power of voluntary movement rapidly and almost fully recovered in the left arm and leg. With recovery of motor power a strong grasp reflex was obtainable in the left hand. At the time of our examinations an unusually firm pressure contact was required to elicit it from either hand. There was no groping and no instinctive grasp reaction. There was no spasticity at the time of our examination. The tendon reflexes on the two sides were equal in both upper limbs, and Hoffmann's sign was not obtained in either. Later operation disclosed an extensive right frontal astrocytoma.

In this case the reflex was not easily elicited and purely cutaneous stimuli had little effect. A strong grasp could however repeatedly be elicited on both sides by a firm local pressure in a distal direction just distal to the proximal interphalangeal joint. When this region was fully anæsthetized in the right forefinger and middle finger by injection of 5 c.c. of 1 per cent novocain, no grasp reflex could be elicited in the proximal finger-joints of these fingers. When the grasp reflex was elicited in the two ulnar fingers the two anæsthetized fingers also flexed and a pull on them then developed a strength of finger flexion as strong as before the injection of novocain. When thus developed, the finger flexion in the two anæsthetized fingers could be maintained after the ulnar fingers were released. The same experiment was performed in a third patient (Case 7, cited in detail later in relation to the instinctive grasp reaction) with glioma in the right frontal lobe. The grasp reflex was abolished in the anæsthetized finger as in the others. In the two last cases the patients were instructed to flex the anæsthetized finger. A pull on the anæsthetized finger then failed to elicit a grasp response yet did so in the unanæsthetized fingers in these circumstances.

From these experiments it was concluded that a stimulus from skin and subcutaneous tissues is necessary for the development of the grasp reflex. The secondary reinforcing effect of stretch of the finger flexors was confirmed and shown to be effective alone once the conditioning response was evoked. Further it was found that when strips of adhesive

tape were attached to the fingers a pull on the tape during the grasp reflex could then alone prolong the response for many seconds. A pull on the adhesive tape alone, the fingers having been previously passively flexed, did not provoke any reaction.

It was also noted in these experiments with local anæsthesia that after the sense of touch was abolished the grasp reflex could be provoked as long as the patient felt pressure. It is therefore probable that stimuli from the subcutaneous tissues are as important for the grasp reflex as more superficial stimulation. It is more difficult to abolish deep sensation from the whole hand, and its retention may explain why Walshe and Hunt (1936) and Fulton (1934) could provoke the grasp reflex even after tactile stimuli were blocked by anæsthetizing the median, radial and ulnar nerves at the wrist. That the moving stimulus is more effective when simultaneously a pressure is exerted on the skin, may indicate that a stretch of some cutaneous or subcutaneous end-organ is necessary. Such an end-organ would have to be oriented to respond to only a distally moving stimulus.

In attempting to localize the situation of the end-organ more closely we applied adhesive tape to the palmar surface of the fingers in Cases 2 and 7. No reaction developed if traction was made on the adhesive tape so as to drag on the skin even when the traction extended the previously flexed fingers. Yet pressure of the observer's finger tips perpendicularly into the palmar surface of the first phalanx could still be an effective stimulus if the pressure moved distally. If the pressure was directed purely vertically against the phalanx no response occurred, even if its application at the same time dorsiflexed the wrist and thus tightened the flexor tendons. We could only conclude therefore that a moving stimulus, in order to be effective, must exert serial distal pressures on some subcutaneous end-organ. In exceptional circumstances, for example immediately following facilitation in one case, it was possible to evoke a localized response by stroking distally with a camel-hair brush with total pressure as little as 20 grammes. More usually a stiffer brush giving pressure of 200 grammes and over was necessary. The necessity for heavy pressure does not necessarily mean that end-organs as deep as periosteum or tendon sheaths are involved, for greater heaviness may indicate only greater intensity, the end-organ remaining relatively superficial. Such stimulation is customarily indicated by the terms "tactile pressure" and "deep sensibility" which in Head's usage (1920) appear to include all contact except light touch. We regard such sensation as exteroceptive in spite of the possibility that it may be mediated by organs such as pacinian corpuscles, which some regard as having proprioceptive function.

It is inevitable that deep pressure will be exerted by the pull on the flexor tendons which elicits the second holding phase of the grasp reflex, but the experiments with anæsthetized fingers or pulling on the fingers by means of adhesive tape indicate that stretch of the flexor tendons alone is necessary to prolong this stage.

When the grasp reflex is elicited by a firm pressure which drags on the subcutaneous tissue but does not entail movement against the surface of the skin the interval between the first, catching, phase and the second, holding, phase of the reflex is very short. When the threshold is high this is the only type of grasp reflex that can be elicited. It is found in some persons without evidence of cerebral disease. Even though the power of flexion of the fingers may be strong this type of grasp reflex is therefore less pathological and less valuable as a clinical sign, than when a lighter stimulus is adequate. The stimulus is most effective when applied over the palmar surface of the proximal interphalangeal joint, and this area may be regarded as the focus of the area of elicitation of the grasp reflex. The usual limits of the area are indicated by the broken line in fig. 1, where its extension deep into each interdigital cleft is not shown.

We may conclude that the adequate stimulus for the grasp reflex is a special combination of cutaneous and proprioceptive stimulation in which a distally moving contact with the skin of specific areas of the palm of the hand or clefts of the fingers conditions a proprioceptive response. In states where the reflex has a low threshold a distally moving light pressure (but not light stationary touch) suffices, and elicits the preliminary grasping movement (catching phase). When the reflex has a high threshold, a more rapid and heavier pressure or drag is necessary. Under these circumstances the proprioceptive pull on the tendons must follow immediately if it is to be effective, and it is often difficult to verify that preliminary movement occurs before the tendons are stretched. Yet in these latter circumstances, the reflex can still be elicited if the fingers and wrist are first passively flexed (fig. 2G), a manœuvre which so slackens the tendons that purely stretch effects are at a disadvantage. Indeed it is characteristic of the grasp reflex that it can be elicited during the lengthening of the flexor muscles of the fingers by a concurrent passive flexion of the wrist. In this it differs completely from simple spasticity.

(*v*) *Analysis of the Motor Response in the Grasp Reflex.*

From clinical observation it was concluded that the grasp reflex exhibited two distinct phases, a catching phase and a holding phase. The more fully developed the response the more readily could these phases be separated. In patients in whom the response was difficult to elicit the

stimulus required to affect a greater area, to exert more pressure, and to move with greater speed. All these factors made it more difficult then to separate the two phases of the reaction. Yet the response still differed from that of a simple pull on the flexor tendons, and such differences could be analysed by cinematographic and electromyographic means.

When the grasp reflex was easily elicited the catching phase could be seen to precede the holding phase in cinematographic pictures. Fig. 2 shows two sequences from Case 6. This patient is reported at greater length in a later section (p. 147) on account of his instinctive grasp reaction. The grasp reflex was very brisk in his right hand, without either spasticity, or increased finger-jerks. The sequence 2A, 2B, and 2C show the initial rapid flexion of the patient's finger to meet the more slowly moving finger of the observer. The sequence 2D, 2E, and 2F which follows 0·5 second after 2C shows the tightening of the grip developed when the fingers of the observer met and pulled on the fingers of the patient.

This is also shown in electromyographic records[1] from Case 6 (fig. 3B) where it will be seen that some small irregular action currents in the flexors of the fingers (from CU *to* P) accompany a very slight muscular tension which precedes the onset of the more regular clonic series of action potentials of the full discharge by 1·0 second. The same weak initial response in another patient (Case 3) is seen in figs. 3A and 3C.

Case 3.—A man of 72 years was suffering from a severe left hemiplegia, due to cerebral thrombosis. He presented a strong grasp reflex in the right hand, in which voluntary movement was not affected. He could open and close the empty hand without difficulty. The tendon-jerks were increased in the right biceps, triceps and supinator but there was no spasticity in these muscles or in the right hand. The fingers offered no resistance to passive extension except a minimal finger-jerk which was, however, greatly increased by a concurrent distally moving contact with the palmar surface of the hand and weak pull on the contracting fingers. A response to prolonged stationary contact (instinctive grasp reaction) was occasionally obtained.

[1]Combined electromyographic and mechanical records were made on moving bromide paper. The electromyograms were obtained by concentric needle electrodes with fixed central core of 0·05 mm. silver wire led to the grid of a Grass amplifying system, the needle being grounded. The output was recorded by Duddell type moving coil galvanometers in a Westinghouse Oscillograph system, kindly provided for us by the National Foundation for Infantile Paralysis for the investigation of various aspects of neuromuscular function. A tracing of the contraction of flexors or other groups of muscles in the forearm was made on the same record by connecting a rubber balloon, fastened over the muscles, by pressure tubing to a rubber membrane manometer with light mirror. The beam from this mirror was focused on the same camera slit with the galvanometer beam. A similar balloon attached to the stimulating finger of the observer recorded through another manometer the pressure applied to the patient's hand.

The initial catching phase was recorded alone (fig. 3E) and was found in three patients to be an irregular short-lasting discharge in the long flexors, especially flexor sublimis digitorum in the case of finger flexion.

When sudden firm pressure was used as stimulus the initial catching phase was shortened, and the response tended to be more clonic in nature. This can be seen in the comparison of fig. 3D from Case 3 with the less abrupt response obtained from the same patient five seconds earlier, fig. 3C. If the reflex was poorly developed, it could be obtained only if the stimulus moved rapidly and exerted firm pressure in the manner already described. In these circumstances the initial "catching phase" was very brief as in fig. 4A from Case 2. Yet the discharge could be intense in the holding phase, as in this instance. If the sudden firm pressure was made over the interphalangeal joint as before, but directed in a proximal direction, no response occurred (fig. 3F), even if the fingers and wrist were passively extended by such a stimulus.

The electromyogram of the grasp reflex was frequently clonic, or broken into a fairly regularly grouped discharge with intervals of relative quiescence (figs. 3B and 3D). The general appearance of such a record resembles in some respects the clonus of the heightened stretch reflex activity of spasticity. Apart from the irregularity of its elicitation and absence of corresponding change in the resting tendon-jerk it presents further differences from spasticity, namely a greater irregularity of rhythm which merges into sustained regular discharge resembling willed contraction, only if the response is very intense (figs. 3A and 4A). When single units could be distinguished the rate of discharge was about the same (20 per second, fig. 5B) as that in willed movement of the same intensity.

In the paretic left hand of Case 2 the grasp reflex was tetanic (fig. 4A). In the non-paretic right arm of the same patient the grasp reflex (fig. 5D) showed a partially clonic pattern. The relaxation of this grasp response closely resembled the delay in relaxation of a voluntary grasp of the same hand (fig. 5E). The clonic feature of the discharge in many patients also appeared in weak voluntary movements.

The muscles taking part in the grasp reflex often changed during the response, probably reflecting a corresponding change in the stress applied to the flexors owing to the movement of the stimulus. Fig. 3A from Case 3 shows a grasp reflex where the two finger flexors co-operated during the whole response, whereas figs. 5A and 5C show grasp reflexes from the same patient where the activity present in flexor dig. sublimis before stimulation disappeared during the response. The late appearance of discharge in the deep flexors in fig. 5B also reveals the same phenomenon.

The extensors of the wrist-joint joined the discharge in forceful grasping (fig. 3B), and if the discharge was clonic the beats in the extensor were slightly later. Sometimes the extensors of the fingers and wrist were quiescent. The extent to which these extensor muscles contributed was consistent with the degree of fixation of the wrist, and this varied with the direction of the pull, as in the same movement when produced voluntarily in a normal person. The part played by the extensors in attempted relaxation of grasping will be described later. The grasp reflex usually began in flexor sublimis digitorum, corresponding to an initial flexion of the metacarpophalangeal and proximal phalangeal joints. If the needle electrode is in the deep flexors this initial phase may be missed and only the proprioceptive holding phase recorded (fig. 5B).

We were never able to satisfy ourselves that a weak voluntary flexion of the fingers could replace the initial cutaneous response of the grasp reflex and allow the proprioceptive factor to develop without previous moving contact. Usually grasping cannot be elicited in this way, and when the exceptional response occurred it was always possible that moving contact had complicated the reaction and had superimposed a true grasp reflex on a voluntary movement. The absence of combination of voluntary and proprioceptive elements in the voluntarily flexed anæsthetized finger was our best evidence that such interaction is not a basis for a grasping response.

Cinematographic and electromyographic analysis therefore confirmed the existence of an initial flexion of the fingers preceding the proprioceptive phase of the grasp reflex, even when such a flexion was so brief that it was difficult to observe clinically. The proprioceptive phase showed an irregular often clonic, type of motor discharge when suddenly and strongly elicited but this often merged into sustained regular discharge resembling voluntary contraction.

(*vi*) *The Relationship between the Proprioceptive Phase of the Grasp Reflex and Spasticity.*

The grasp reflex is most usually found in the absence of the phenomena of spasticity. Occasionally however some spasticity is also present. It was necessary therefore to distinguish between these two phenomena particularly since the electromyogram is often irregular and clonic in both. From the purely clinical point of view both present an active resistance to passive extension of the fingers of the hand, but there are striking differences.

Spasticity is felt as a resistance to passive lengthening of the finger

flexors which in any given case is elicited at a fairly constant length provided the speed of extension is kept constant.

The resistance is more easily elicited the more rapid the passive extension is made. The more intense the spasticity the earlier in the passive movement the resistance is felt. The resistance rises rapidly to a maximum and then, within 0·5 to 5 seconds according to its intensity, it melts away with increasing speed (lengthening reaction, clasp knife phenomenon). It can be then renewed only by a renewed passive flexion followed by a repetition of the full movement of passive extension. Except in its most intense degree spasticity requires some preliminary lengthening of the affected muscle, and thus appears only at an interval of time after the passive extension movement has begun. Its relationship to a given length of the flexor muscles is well shown by the greater ease with which it can be elicited when the wrist is extended, and its abolition or late appearance when the wrist is held flexed.

The clinical manifestations of the grasp reflex present differences in all these criteria. The response could be obtained in association with any posture of the wrist whether the flexor muscles were stretched by previous extension, or lengthened by almost full flexion of the wrist. According to the location of the cutaneous stimulus exciting the grasp the proprioceptive phase could be induced in any position of the finger. Increase in speed of the distally moving stimulus increased the speed of grasping within a limited range. The grasp reflex could be elicited at slower speeds of movement than could mild or moderate degrees of spasticity, but very rapid passive extensions of the fingers such as could readily give rise to a jerk of contraction in spastic muscles usually failed to elicit a grasp reflex. The resistance to passive extension caused by the grasp reflex was sudden and rose further in the next second, thereafter being steadily maintained for a further interval. When it waned it was immediately renewed by a sudden increase in the passive pull without change in position. Finally, the grasp reflex, unless only feebly developed, did not require a preliminary wide angle of passive extension of the finger-joints. Indeed it could be elicited during the movement of passive flexion of the wrist, while the flexor tendons were being slackened. The same manœuvre did not result in any flexion of the fingers in the spastic hands examined by us.

Passive extension or flexion of the fingers of a hand exhibiting the grasp reflex does not usually meet any resistance unless a moving contact is also made with the specific area of the palmar surface. To avoid such contact the fingers were held by their distal extremity, pulled upon by

adhesive tape or held in a thick cloth. Spasticity on the contrary did not change when the fingers were held in this way. In a patient with moderately severe spasticity in the hand resulting from a mid-brain lesion we were able to demonstrate that complete anæsthesia of the middle finger induced in the same manner as in our method of investigating the adequate stimulus for the grasp reflex made no difference to the spastic resistance in this or the other fingers.

Spasticity is associated with an increase in the tendon-jerk of the finger flexors whether elicited as Hoffmann's sign or by tapping on the partly flexed fingers. In most patients exhibiting the grasp reflex the finger-jerk was minimal in degree and was not clonic. The electromyogram of the finger-jerk nevertheless showed a small action current followed by a silent period (fig. 4B). If in the process of eliciting the finger-jerks the examiner made also a moving contact with the proximal palmar surface of the digits a small grasping movement was added, and during this the finger-jerk became greater in intensity and was often clonic (fig. 4C). Clinical observation also showed that a Hoffmann's sign could be facilitated by palmar contact in patients with the grasp reflex, and it is of further interest that under these circumstances the two fingers next to the finger stimulated often alone showed the jerk response. In these ways the facilitating effect of the cutaneous phase of the grasp reflex on the proprioceptive reflexes was further documented.

In order to compare the grasp reflex with the simple proprioceptive reactions in the flexors of the fingers a patient suffering from a spastic quadriplegia from cervical cord lesion was examined electromyographically. In this patient hyperactive finger-jerks and finger clonus could be elicited with ease but there was no grasp reflex. The effect of a moderately rapidly alternating passive extension and flexion of the fingers is shown in fig. 6A. As the speed and range of the extension movement increased, the flexors of the fingers showed clonic bursts of contraction. Such a proprioceptive response arose late in the stretching movement and tended always to subside during the movement. A lengthening reaction began to occur within 1/5 second of the beginning of the response to the stretch of the flexor tendons. A certain fairly wide angle of passive extension had to occur before the flexor muscle responded, even to rapid stretch (fig. 6B). The spastic response, therefore, was late in appearance and reached an early maximum following which it declined rapidly even when passive extension continued. In some extremely spastic patients a sustained finger clonus could be elicited but it was then invariable in appearance at the same muscle length and whatever the nature of the stimulating movement.

If a passive pull on the flexor tendons were superimposed on a weak voluntary movement in a patient with spastic quadriplegia a slight heightening of the proprioceptive response occurred (figs. 6C and 6D), with intensification of the initial clonic beats. The response then either declined rapidly, as did the proprioceptive response when elicited alone (fig. 6C), or fell away to a tonic plateau. In the latter case the ability of the patient to relax when suddenly ordered to do so showed that the tonic phase of the response had become a voluntary movement (fig. 6D).

Such studies demonstrated that the resistance of spasticity when it occurs in the finger flexors is a passive phenomenon lacking a number of features exhibited by the grasp reflex.

(vii) Voluntary Release of the Grasp Reflex.

The natural termination of a grasp reflex was a gradual decline after some seconds in the absence of a change of stimulus. The grasp reflex is however characterized by a difficulty in voluntary relaxation, and attempts by the patient to release his hand may result only in greater persistence of the grasping. This difficulty is most apparent when the response to the adequate stimuli is fully developed.

The finger movement which indicates the first phase of the grasp reflex ends as soon as the moving touch on the skin ceases. It is ill-sustained and brief. There is no question of difficulty in relaxation owing to its essential brevity. An active extension of the fingers by the patient during this phase may, if well timed, abort the reflex response. The inability of the patient to relax appears only when the first phase is followed by the second (holding) phase, relating to a lasting pull on the contracting fingers. Usually the grasp was more difficult to relax the more completely the second phase was developed.

It was much more difficult for the patient just to stop the contraction than to get rid of the stimulating object by actively stretching the fingers. In the few patients who were sufficiently co-operative and attentive to make an attempt to relax the grasp reflex without innervating the extensors it seemed that only a weak response could be terminated in this way. Two of our cases had an active grasp reflex in a hand paralysed for voluntary movement. Such paralytic patients could neither prevent nor release the grasp reflex.

Case 4.—A woman 65 years of age had gradually developed a spastic paralysis of the left arm and leg in the previous five years. Convulsive seizures of Jacksonian type had occurred in the left side at intervals in this period. In the last two years the fingers of the left hand had gradually assumed a clawed posture. At operation

a parasagittal meningioma was removed from the right frontal region extending from the precentral gyrus anteriorly for 4 cm.

Examination three days after operation showed the presence of severe weakness of the left hand so that the patient could make a just perceptible flexion movement of the fingers if there was no resistance, and was unable to move any single finger separately. Passive extension of the fingers encountered a weak resistance which was not sustained. There was a moderate degree of spastic resistance to passive extension of the left elbow-joint. The biceps and supinator jerks were very brisk on the left side and a brisker finger-jerk was present in the left hand than in the right. The plantar responses were both extensor. There was a mild generalized atrophy of the muscles of the left arm and leg, with some œdema. A weak grasp reflex was provoked twice in about twenty minutes on this examination, and twice during a more brief examination three days later. The resistance obtained was much stronger than was encountered in the spastic resistance to simple passive extension, or in maximal voluntary effort. Spastic resistance was strongest with the wrist fully extended, and even then was felt only when the fingers were nearing full extension. The grasp reflex on the contrary appeared with flexion of the wrist and was associated with sudden flexion of the fingers to meet the stimulus.

The grasp reflex showed increase in ease of elicitation and also in strength in the following two weeks, whereas spasticity became somewhat less. The patient could not influence the grasp reflex during the first two weeks after operation. After three further weeks when power of voluntary flexion of the fingers had recovered to approximately 50 per cent of that of the other side the patient could prevent the grasp reflex when requested to do so but could release an established grasp response only after long delay. The plantar response was still extensor and the tendon-jerks still remained overactive on the left side. No grasp reflex of the toes could be elicited, and no instinctive grasp reaction was obtained, at any time. The patient was alert and co-operative in all examinations.

Case 5.—A 23-year-old man with severe head injury, suffered from stupor, aphasia, and paralysis of the right arm with weakness of the right leg following the injury. At operation a large extradural hæmatoma was removed from an area covering the lateral aspect of the left frontal lobe.

Neurological examination four days after operation revealed a persisting complete paralysis of the right arm and severe weakness in movements of the right leg. The tendon-jerks were moderately increased in the right arm and leg, and some mild spastic resistance was left on passive extension of the right elbow. There was little if any resistance to passive extension of the fingers. The plantar responses were both flexor. There were no reflex changes on the left side. He was mildly confused then and for the remainder of the first post-operative week, but his motor aphasia then cleared and he began to read a newspaper on the ninth day.

On the fourth day a grasp reflex could be provoked by repeated firm distally moving pressure from the palm of the right hand over the palmar aspects of all four fingers. The reflex, though difficult to provoke, could resist powerful traction. It was soon fatigued by rapid repetition for more than three or four times.

The left limb showed no neurological abnormality, but a fairly strong grasp reflex, with fragmentary responses to localized stimulation, was present in the left hand.

After the first four days the grasp reflex in the right hand increased rapidly with concurrent return of power of voluntary movement which was estimated to be approximately 50 per cent of that in the left hand by the tenth day. The patient was then still unable to prevent the grasp reflex on either side but could release it on the left side by an extension of the fingers. In the following days he began to release the grasp reflex also on the right side by extending the fingers.

A grasp reflex of the toes was present on both sides at all examinations and was more fully developed on the left ("normal") foot.

Fragments of the instinctive grasp reaction could be elicited from the left hand, but not from the right.

In some patients there was great difficulty in relaxing the response even though voluntary effort was almost fully retained. Apart from such exceptions there was in general a lessening of ability to release the grasp reflex in proportion as the voluntary power of voluntary innervation of the muscles was lessened.

Many patients could actively extend the fingers during a grasp reflex which was fairly strong, but the process was not a simple one and probably resulted from the avoidance of fresh flexor stimulation. That this difficulty was related to the proprioceptive stimulation in the second phase was shown by the greater inability to release the grip when the pull by the observer was intermittently varied in strength. Thus by "shaking hands" continually it was possible to prolong the grasp reflex indefinitely in many patients. The fingers of the patient then steadily performed fresh grasping movements.

Even if a more constant pull was made on the fingers release could be made difficult if movement of the stimulus was allowed. For example, in Case 1 the reflex was provoked by putting the handle of a pail of water into his hand. When he was then asked to relax it was obvious that the fingers performed a series of grasps, each grasp more distally than the one before. The pail at the same time sank towards the floor in a series of small steps, and was finally released only after a few seconds. In this and some other patients reflex grasping was also provoked by moving a handle against the palmar aspect of the fingers. A load was attached to the handle so as to give a constant pull on the fingers once the reflex had been elicited. The activity remained steady for several seconds if the pull was even, as shown in accompanying electromyographic tracings. When the subject was asked to relax a series of lessenings and sudden increases in electrical activity paralleled the partial relaxations and renewed pulls of the fingers. During the appearance of each new grasp the electromyogram showed increased activity, and then the activity was again steady until it lessened as the grasp declined, only to be replaced by a further grasp. These experiments showed that during a prolonged grasp there must be an adaptation to afferent stimuli and that new impulses are constantly needed in order to maintain the grasp reflex. Delay in termination was thus related to renewed stimulation of the reflex.

Relaxation of a willed grasp of the empty hand of a normal person is associated with an abrupt cessation of the intense action-current discharge

in the flexors. There is a sudden electrical silence followed usually by the appearance of further activity after about 1/5 second (Denny-Brown and Nevin, 1941; Denny-Brown, 1948). If the willed cessation is forceful an

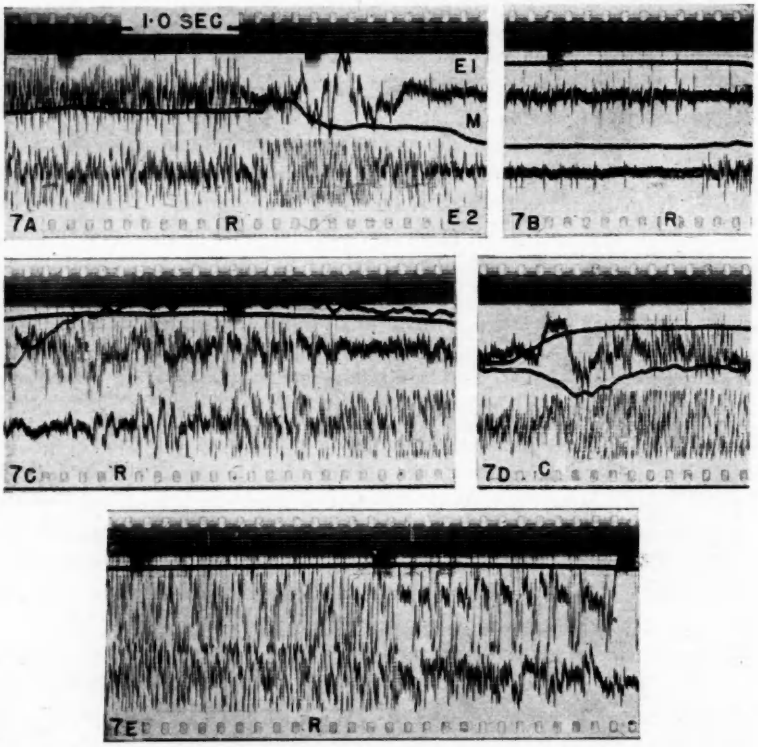

FIG. 7.—From Case 2. Right non-paretic arm. Upper EMG (E_1) from m. flexor profundus digitorum, lower EMG (E_2) from m. extensor communis. 7A: The record begins during a voluntary closure of the hand. The mechanical tracing (M) shows the bulk of the whole forearm muscles and here records both extensor and flexor activity. When the patient is told to relax the grasp at R, the extensor (E_2) shows a burst of contraction after a short quiet interval. The flexor (E_1) shows sways due to electrode movement, but very few action potentials. 7B: The events are as in fig. 7A, but the initial voluntary grasp was weak. The flexor-extensor relationship was the same. 7C: As fig. 7A but the record begins during a grasp reflex. The patient attempted to relax suddenly at R. The activity of the extensors increased rapidly, but the flexor discharge diminished only very slowly. 7D: Shows the attempted initiation of a grasp reflex at C. The patient had been told to attempt to prevent a response, which she did by contracting the extensors. 7E: Shows a strong grasp reflex in progress and an attempt to relax at R without extension.

intense but brief burst of discharge occurs in the extensor muscles about 1/10 second after the abrupt cessation of the main flexor contraction. In the limb of a patient with a mild grasp reflex, but with full power of voluntary movement, a willed closure of the empty hand, followed by a sudden willed opening of the hand, showed these normal electromyographic phenomena (fig. 7A). This sequence of events was still present if the willed closure was weakly performed (fig. 7B). An attempt by the patient to relax a grasp reflex in the same hand revealed a different state of affairs (fig. 7C). The contraction of the extensors slowly gathered momentum and was almost fully developed before the flexor contractions showed any lessening. After a period of conflict the extensor contraction gradually increased as the flexor contraction slowly and irregularly faded. If there was a slip in the pull on the fingers as relaxation occurred a final large clonic beat was seen in the electromyogram; as in figs. 3A and 3C. When the fingers gave way during a more uniform stretch there was a slow diminution in the response.

Apart from the difficulty in voluntary movement introduced by the grasp reflex, or by coincidental hemiparesis, the willed movements of the fingers and hand were not disordered. For example, if Case 1 were asked to open and close his empty left hand (which had a strong grasp reflex) he could do this as rapidly as with his normal right hand, provided he avoided contact with the palm of the hand each time he closed the fingers. He could also do this if an object was lying in his hand, but the opening of the hand was sometimes delayed if the fingers touched the object during the opening of the hand.

If a patient gripped two of the observer's fingers the patient could relax the grip immediately as long as the observer did not move his fingers. If during such a grip the observer pulled on the patient's fingers and then suddenly ceased to pull, the observer first felt an intensification of the grip on his fingers (the grasp reflex) followed by a very rapid decrease to zero. The patient was then able to open his hand as rapidly as when it was empty but not before the pull ceased. The grasp reflex may therefore develop during contraction initiated voluntarily and in estimating the power of voluntary flexion of the finger it is necessary to avoid stimulating a grasp reflex. Rarely the grip waxed and waned for some seconds after the observer's pull had ceased, a phenomenon observed by Adie and Critchley (1927), but we found that this was related to the presence of another phenomenon, the instinctive grasp response.

That the grasp ceased at the moment the observer stopped pulling, even though his fingers remained in the patient's hand, indicates that for

maintenance of the grasp reflex it is not sufficient that the grasping fingers meet resistance (as supposed by Halverson, 1936). A passive pull on the contracting muscles besides the distally moving pressure is necessary.

Some patients occasionally could not let go a fixed object, such as a door handle, and at other times could do so without difficulty. The reason appeared to be, not that the grasp reflex varied so much in strength, but that in some attempts to release the grip voluntary relaxation was not complete before the patient began to withdraw his arm. A moving contact and further pull of the fingers resulted. Such stimulation of the grasp reflex was avoided when the grip was well relaxed before the movement of the arm began.

We concluded that much of the difficulty in voluntary release of the grasp reflex was due to the ease with which fresh reflex stimulation renewed the response. Voluntary release was usually associated with extension of the fingers, which persisted some time before it was effective. The mechanism was presumably that extension, though unable forcibly to overcome the flexors, acted in lessening the opportunity for further stimulus. In some co-operative patients there appeared to be some ability to inhibit the flexors of the fingers without innervating the extensors. The complete inability of paralytic patients to influence the grasp reflex indicated absence of both these mechanisms.

(viii) Prevention of the Grasp Reflex.

Usually the grasp reflex was easier to provoke when the attention of the subject was distracted. Thus in many patients and even in some normal subjects the reflex was easily provoked when they were concentrating upon other problems, whereas it was almost impossible to elicit when they had their attention on the examination. It was easier for the patient to avoid grasping when he had an opportunity to watch the examination, probably because he could anticipate the stimulus by a small movement of extension of the fingers. When directly asked to avoid the grasp reflex, many patients with moderate degree of reflex could do so even if the reflex was otherwise easily provoked. After such a request some of our patients could avoid the grasp reflex for 10 to 20 seconds, but then the response occurred as before. Whether they were unable to concentrate their attention or were unable to perform the contrary effort for a longer period was not clear.

In eliciting the grasp reflex one should therefore try to avoid the attention of the patient by suddenly pulling on his passively flexed fingers when talking to him about other subjects or asking him to close his eyes

firmly. It was usually more effective to distract a patient than to ask him to relax, for many patients with mild or moderate degree of reflex seemed to be able to avoid a grasp response by simple relaxation. For a patient who had a well-developed grasp reflex the most effective way to avoid grasping was to keep the fingers actively extended during the examination. Successful evasion of the reflex was in most cases associated with active intense innervation of the extensor muscles of the fingers (fig. 7D).

A few patients were quite unable to prevent the grasp reflex, even when they were alert. Thus Case 5 with extradural hæmatoma was unable to prevent or release the grasp, not only in the right paralytic arm but also on the left, almost normal side. Case 4 with a paralysed arm could not influence the response even with the eyes open, but could do so when she had recovered from her paralysis. It has already been mentioned that some patients were able to prevent the grasp reflex by relaxation alone, without any visible extension of the fingers. We found no separation of these mechanisms in paralytic patients, who lacked both means of control.

We found that release of the grasp reflex was also concerned with ability to prevent fresh stimulation and a general correlation found between ability to relax the grasp reflex and ability to prevent it was therefore to be expected. Some exceptions were found. For example, some patients could prevent the reflex but were almost unable to let go when it was elicited. The strength of the proprioceptive phase of the reflex is relatively independent of ability to prevent or relax the reflex. This discrepancy between the strength of the grasping contraction and the ability to prevent and relax may be explained by assuming that the strength of the proprioceptive response is relatively fixed, whereas the ability to prevent or relax depends on other factors such as ability to concentrate, the effect of training, and power of movement. In paretic patients the strength of the response when pulling on the fingers was usually much greater than was full power of willed flexion of the fingers.

We concluded that ability to prevent the grasp reflex was an important factor in estimating its degree of development.

(*ix*) *The Effect of Stimulation of the Dorsum of the Hand.*

If a stimulus similar to that used for provoking the grasp reflex were applied to the dorsal side of the hand, no reaction developed. In many patients the response lessened considerably when the observer stroked the dorsal side of the hand in a distal direction and at the same time stimulated the corresponding part of the palmar side of the hand in the

ordinary way. Also when the observer grasped the finger of the patient, touching both the ventral and dorsal aspects and performed passive movements, the grasp reflex very rarely developed. In agreement with Walshe and Robertson (1933), we found that usually the grasp reflex would not develop if the patient's hand, palm uppermost, rested in the observer's palm. If, however, only the proximal part of the patient's fingers were supported during the stimulation, the grasp reaction could be provoked in the distal interphalangeal joints. If the observer when supporting the patient's hand in this position at the same time squeezed the hand, the grasp reaction never developed. This test could be useful in deciding if a finger flexion is "voluntary" or not.

When the grasp reflex was fully developed, pressure by gravity on the dorsal side of the hand and fingers was of less effect. In some patients (for instance Case 1) one could then cause release of the grasp reflex by a firmer pressure on the dorsal side of the grasping hand or fingers. During a fully developed grasp reflex the strength needed to release one of the fingers passively was remarkably slight. The contraction of the remaining fingers then often seemed to increase as if to maintain the same strength of the grasp reaction.

In infants lying awake with the hands clenched we found that stimulation by a light touch on the dorsum of the hand caused an extension of the fingers in some cases followed by the closing phase of the instinctive grasp reaction. Such interaction of two reflex effects might explain the inhibiting effect of the dorsal stimuli. The inhibition of the grasp reflex by stimulation of the dorsal surface of the hand favours the point of view that the reaction is a true reflex.

(*x*) *The Grasp Reflex of the Toes.*

The reflex is best elicited by using the side of a rod such as a pencil or the shaft of a reflex hammer and exerting firm pressure against the sole of the foot, at the same time moving distally toward the toes. If the reflex is strong, there is a flexion of the toes as soon as pressure is exerted against metatarsophalangeal joints. If the actively bent toes are pulled upon, the contraction suddenly increased in strength to such an extent that the foot could be lifted in the air before the toes loosened. We found that if the stimulating object were drawn ventrodorsally through the interspace between the bases of two toes, the toes would adduct and compress the object. The reaction was the same for all the toes and a local flexion reaction could be provoked in each toe. Such local reactions were not so completely differentiated as in the fingers.

In all, 34 patients with a grasp reflex in the hand were examined. In no case could grasping of the toes be demonstrated where some finger grasping was not also present. In 6 patients the grasping of the toes was stronger than in the fingers. More often toe grasping was weaker than finger grasping (16 patients). In 15 patients in whom finger grasping was of unequal strength on the two sides, the grasp reflex in the foot was more strongly developed on the side of greater response in the hand.

Of the 17 patients with a strong pathological grasp reflex for the fingers only one case failed to show the grasp reflex of the toes. In 4 of the 17 patients with weak finger grasping no reaction of the toes could be observed. In Case 1 with strong grasp reflex in the hand, the grasping of the toes failed to appear on some of the days he was investigated. In infants the grasp reaction of the toes was very well developed, in most cases corresponding to the strength of the finger grasping.

It was concluded that the same kind of stimulation of the foot as for stimulation of the grasp reflex in the hand elicited a grasp reflex in the toes. There was evidence that the grasp response of the toes was a summation of a series of local reactions as in the fingers. The lack of opposition of the big toe is clearly related to anatomical circumstances and warns that opposition *per se* is not an essential feature of the physiological grasp. We did not in this material find any "tonic foot response" lasting longer than the stimulus. By pressing on the distal sole of the foot in the manner described by Goldstein (1938) we found, however, a strong plantar flexion of the four lateral toes in several of our patients. This reaction seemed in 12 especially observed cases to be correlated with an increase of the normal plantar response, but had no distinct correlation with the grasp reflex as we have described it.

(*xi*) *The Relationship between the Grasp Reflex and other Reflexes.*

In 12 patients with a well-developed grasp reflex, *"reflex" sucking* was elicited by a contact with the lips in 5, and was associated with opening of the mouth and partial turning of the head. In 4 of the others there was only a slight protrusion of the lips in response to such contact. Sucking did not appear at all in the remaining 3 patients with a strong grasp reflex. In 7 patients with a weakly developed grasp reflex there was a sucking response in 3 cases. When the grasp reflex was unilateral the sucking appeared only on the same side. In one patient, during recovery from a cerebral thrombosis, a unilateral sucking reflex became more easily elicited as the grasp reflex decreased in strength. These two reflexes were thus closely but not directly associated.

Practically all the patients with a positive grasp reflex had *some resistance to passive movement* in the elbows. The resistance was mild in degree and gave way toward the end of a passive movement. It varied greatly in strength during an examination. This resistance had the same characteristics as the resistance during passive movement found in many normal persons, commonly called a "difficulty in relaxation." In Case 1 this resistance was greater on the same side as the grasp reflex, but generally there seemed to be no definite correlation between the strength of the grasp reflex and the degree of the resistance to passive movement. Since the resistance appeared more frequently than in normal persons and often was stronger, it is possible that in many cases it is a release phenomenon related to the grasp reflex. In this we are in agreement with Kleist (1927) and with Schaltenbrand (1940). The latter measured the resistance to passive movement by means of a special apparatus. He often found the form of variable resistance called "Gegenhalten" by Kleist (1927) on the same side as the grasp reflex. He therefore supposed this resistance to be an organic symptom most often caused by a frontal lobe lesion. Kleist (1927) had postulated a thalamic lesion. This resistance was not that which is called spasticity for it does not correlate with changes in tendon reflexes. Further, the patient can influence it and bring about considerable variations in its degree. It was sometimes tremulous and a "frontal tremor" was then present in the outstretched limbs. It appeared in some patients to be related to a tendency of the affected limb to assume and hold a chance posture involuntarily for many minutes (catatonic attitude).

The appearance of the grasp reflex was not related to any corresponding increase or decrease of *tendon reflexes.* In a few patients it was possible to elicit reflex grasping in a paretic limb when the tendon reflexes were augmented, but in ordinary cerebral vascular lesions with spastic hemiparesis the grasp was found only on the non-paretic side as noted by Schuster and Casper (1930). Walshe and Robertson (1933) also found that the grasp reflex could not be explained by a spasticity alone. Indeed it would appear that beyond a certain degree spasticity is not compatible with the grasp response.

No correlation between the *plantar response* and the grasp reflex in the foot was found. In one patient with toe grasping, a flexion of the great toe, provoked by the stimulus used for the plantar response, could be prolonged by a pull on its plantar aspect. It is possible that the normal plantar response is in some way related to the grasp reflex of the foot, but reinforcement by passive pull (grasp reflex) is very rare. A very active Babinski extensor response naturally acts in opposition to toe grasp-

ing but both could be present together if the Babinski were obtainable only from the outer border of the foot.

In 15 cases presenting a strong grasp reflex *Meyer's reflex* (adduction and opposition of the thumb in response to forced passive flexion of the second finger) was increased in 11 in the hand which showed grasping. In 10 cases of weak grasp reflex the Meyer's reflex was increased in only two cases. This relationship is in agreement with the findings of Adie and Critchley (1927).

Only two patients with a strong grasp reflex showed a positive *Hoffmann's* sign. Since Hoffmann's sign is related to increased tendon reflexes, the absence of correlation was to be expected.

We have expressly sought for clinical evidence associating the grasp reflex with the *tonic neck and labyrinthine responses of Magnus and de Kleyn*. In no single case were we able to convince ourselves that the grasp reflex or any of its phases could be varied in strength or ease of elicitation according to the side on which the patient lay or the side to which the head was turned. Three patients presenting positive changes in attitude according to the position of the head and body had no grasp reflex. These reactions to change in position of the head were usually evident in the shoulder and elbow, but one of the patients showed slight extension of the fingers of the hand on the side to which the head was turned. One other patient was of particular interest in that a spastic hemiplegic hand caused by the presence of a thalamic glioma showed an obvious increase in clawing with considerable increased resistance to passive stretch of the fingers when the patient lay on the opposite side, or had her head turned to the opposite side. When this patient lay on the side of the hemiplegia the spastic clawing of the fingers and associated finger-jerks were almost completely absent. Yet sensory stimulation of the hand elicited no trace of grasping in either posture.

We therefore conclude that whereas the grasp reflex may be occasionally associated with increase of tendon reflexes and other evidence of spasticity the two phenomena are separate and, in full development, incompatible.

IV. The Instinctive Grasp Reaction.

(i) *General Description.*

The first case cited in the above account presented a stereotyped response to stimulation of the hand, the grasp reflex. More usually patients who exhibit involuntary grasping phenomena show less predictable and more modifiable responses, either in addition to the grasp reflex or without it. These responses, which we shall call "the instinctive grasp reac-

tion," include an adjustment of the fingers and hand to the stimulating object preliminary to a *"final grip."* The most simple form of this adjustment, a phase which we call the *"closing reaction,"* was a sequence of movements of the fingers to surround the object. If the end of a finger was stimulated the closing reaction began with a palpating movement of this and the other fingers, followed by small movements of alternate grasping and extension ("climbing") movements. If the first contact was made on the dorsum of the hand a rotation of the hand began the closing reaction. The sequence of closing movements usually brought the stimulus to the centre of the palm by a complex adjustment, the details of which depended upon the initial point of contact. Owing to this preliminary adjusting phase the final grip was a co-ordinated grasp of all the digits.

The closure of the fingers was often delayed in onset and was usually made by a series of weak and intermittent flexion movements. The strength and speed of the closing reaction were variable and not proportional to the pressure of stimulating contact. The most effective stimulus was a light stationary touch on sufficient area of the skin of any part of the hand. When the reaction was weak it could only be provoked by touching the radial part of the hollow of the hand, whereas if it was stronger it could also be elicited from the ulnar side of the palm, the ends of the fingers and the dorsum of the hand, parts which were insensitive to the grasp reflex.

The final complete grip did not invariably follow the closing reaction, which might be repeated for many minutes before a final grip developed. The hand would often open spontaneously after some closure reactions, but if the stimulus tended to move in any direction suddenly the patient's fingers immediately tightened, even if the grip had been very loose. We shall call this the *"trap reaction."* This sudden tightening appeared just as the object in the hand started to move and often before there was any pull on the flexed fingers. If the patient did not succeed in holding an object as it was pulled away from the hand during the closing reaction, the hand and fingers moved to follow and keep contact with the retreating stimulus. If for instance the stimulus was pulled out of the hand over the ulnar side of the fifth finger the hand would follow in an ulnar direction. The presence or absence of vision made no difference to this *"magnet reaction"* of Schuster. Contrary to the findings of Walshe and Robertson (1933) we succeeded in eliciting this "magnet reaction" in cases of deep semi-coma. If the observer, having elicited a magnet reaction, allowed the pursuing hand to touch the stimulus and then moved it fur-

ther away he could prolong the pursuit. The patient's empty hand would then often perform small grasping movements while thus feeling after a retreating stimulus. This phase of the reaction, which we call *"instinctive groping,"* is identical with the "forced groping" of earlier authors. In a few patients the pursuit phase of the instinctive grasp reaction could be prolonged or reactivated by a visual stimulus.

The following cases will illustrate different degrees of the instinctive grasp reaction:

Case 6.—Male, 85 years. Diagnosis: Arteriosclerotic heart disease with mild decompensation. Multiple small cerebral thrombosis. Melæna. Left hemiplegia. The patient answered simple questions and obeyed simple commands. He was mildly disoriented but co-operated well. Sometimes he was drowsy and it was then a little difficult to communicate with him. When he was not drowsy, some motor restlessness was observed. When asked why he gripped the observer's hand he sometimes said, "I am so glad to see you." When he was asked to shake hands he sometimes continued the movement several times (? perseveration). Motor power in the right arm and leg were of normal degree, whereas the left arm was almost completely paralysed, except for some feeble movement of the shoulder. There was severe weakness of the left leg. He was negativistic and tended to resist any attempts to move the right arm at the shoulder or elbow. There was no spasticity in the right hand. The finger-jerks were not obtainable in the right hand, and the right biceps, triceps, and supinator jerks were not increased. On the left side there was moderate spastic resistance with increased tendon-jerks.

Abnormal responses in the right arm: The right hand showed groping movements and, when the groping did not disturb the examination, a distinct grasp reflex could also be elicited. On the first occasion he was examined, the local reactions of the grasp reflex were well developed, with a rapid clonic tremor. Electromyographic records were made of these. Grasping seemed sometimes to increase when the patient had his attention on the observer as compared with when he was distracted by another person. Meyer's reflex, the sucking reflex, and the grasp of the toes were not investigated.

The instinctive grasp reaction: When the patient was more drowsy at the beginning of the examination a slow intermittent closure of the hand terminating often in a firm grip could be elicited by touching the radial part of the palm steadily with the examiner's finger. As he became more alert during the examination, the ulnar side of the palm also responded to a stationary touch. At the first examination groping could be elicited also by touching the dorsum of the hand and occasionally the lower part of the forearm. The response was not constant in speed, degree, or ease of elicitation. If he was distracted by some discomfort in posture it was difficult to get any response, but the groping increased remarkably if he engaged in conversation.

Usually he did not look at the groping hand, and when his eyes were blindfolded for a period there was no decrease in response to touching the hand. When the observer placed his fingers in the middle of the palm, the hand just closed slowly and deliberately. The movement did not show the clonic tremor which was present in the grasp reflex in the same hand. The grip usually began very loosely, and the hand reopened once or twice before it finally squeezed very hard. The strength of grip was then as great as when one asked him voluntarily to squeeze one's hand. If the observer's fingers touched the patient's finger tips, a climbing

movement up the observer's hand began, and in three to four light grasping movements succeeded in bringing the observer's fingers completely into the patient's hand (fig. 8). At this moment the examiner's hand was squeezed very firmly.

When the examiner slipped his fingers in between the patient's slightly flexed thumb and forefinger, the patient often gripped very strongly with all fingers as soon as the observer's fingers touched the skin of the fingers on the way into the palm (the "crab claw" reaction of Adie and Critchley). Sometimes this entering grip did not occur and then the weak localized finger flexion characteristic of the first phase of the grasp reflex could be observed during subsequent withdrawal of the stimulating fingers. If the ulnar part of the palm was first to be touched there was an ulnar deviation of the wrist before gripping, bringing the patient's hand

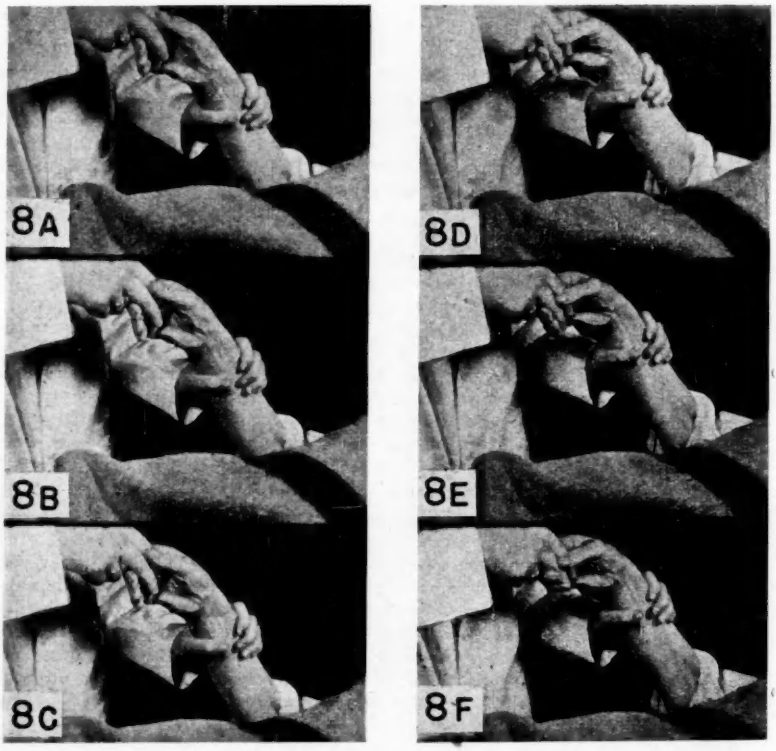

FIG. 8.—Two series of cinematograph pictures from an examination of Case 6 to show the elicitation of the instinctive grasp reaction by the introduction of two of the examiner's fingers into the hand of the patient, who is blindfolded. The series 8A, B, C is followed by 8 D, E, F after an interval of 9 frames (0·6 second). The examiner's fingers first make contact before fig. 8A and then are held still. The patient's fingers begin a series of small grasping movements one of which begins in fig. 8A and is complete in fig. 8F.

into a posture better adapting the grasp to the object. If the dorsal surface of the hand were touched the hand gradually turned around in several movements each of which made further contacts, bringing it into an appropriate position to grip the stimulating fingers.

He always grasped with all the fingers, even if the stimulus were applied to the ulnar part of the palm. The thumb would then be strongly adducted to meet the stimulus. If the observer squeezed the dorsal aspect of the patient's flexed but empty hand during a grasping movement the grasping ceased immediately.

When the observer withdrew his hand while the adjusting movements were developing, the patient followed the observer's hand in the direction of withdrawal. If his hand were then touched repeatedly it could in that way be made to move through space in the direction of repeated withdrawals (the magnet reaction). The patient made continuous small grasping movements with his hand during this pursuit of the stimulus. If it failed to make immediate contact, the patient's pursuing hand fumbled around in space as if feeling in darkness. However, he did not look at his hand or the observer's hand, and the reaction was not abolished by covering his eyes. Once he held his hand up in the same position for many seconds performing small grasping movements. This occurred when we had teased him for some time by repeatedly withdrawing the stimulus. We never observed the hand pursuing a moving object unless it had touched the hand just before. As mentioned above, it made no difference to any of these groping movements if he was first blindfolded.

Sometimes he withdrew his hand, trying to escape the observer's hand. The first day of examination it appeared that he could prevent the groping by clenching his hand, so that the observer could only touch the dorsal side of his hand. If the observer succeeded in touching his palm, a grasping movement always followed.

The patient sometimes spontaneously suddenly opened his hand during a strong grip but did not usually release his grip when he was asked to do so.

When the patient's fingers were closed around the examiner's, a tightening of the grip (trap reaction) immediately appeared if the stimulating fingers made any movement to withdraw. If the patient's fingers were loosely flexed around the stimulus in his palm, the tightening clearly began to develop as the escaping contact touched the skin and before the observer had performed any stretch on the flexed fingers. The tightening usually was very firm and there was not, as in the grasp reflex, any correlation between the force used for withdrawing the hand and the strength of the patient's grip.

Case 7.—A woman of 35 years of age, who suffered from a right frontal astrocytoma probably involving the corpus callosum, showed a facile grasp reflex and most of the phenomena of instinctive grasping as well. She was slightly disoriented and euphoric before operation, but co-operated well in our examinations. There was a slight weakness of the left side of the face but no demonstrable weakness in the limbs of either side. The tendon-jerks were present and equal in the upper limbs, but were slightly increased in the left lower limb. An extensor plantar response could be obtained only from the outer border of the left foot. No sensory defect could be found. There was a fine irregular tremor of the outstretched hands, more marked in the right side. She tended to hold the left arm and hand for periods up to one minute in any posture passively imposed upon them, if her attention were directed elsewhere. She had no difficulty in relaxing a voluntary closure of the left hand or in other voluntary movements of the left limb. Though the patient appeared surprised and embarrassed when her attention was drawn to an unusual posture or behaviour of the left hand or limb, she was fully able to name its various parts, to perform small movements of the hands when requested, and showed no evidence of motor apraxia.

Appropriate stimulation of the left hand revealed a highly developed grasp reflex, obtainable in any single digit. Using a small brush as stimulus small closing movements could be elicited with ease with pressures as light as 200 grammes. She could avoid a response for about one minute but they could then be again obtained. She was unable to relax the proprioceptive phase if the passive pull was maintained. Anæsthesia of one finger resulted in the loss of response in that finger, though full power of voluntary flexion was retained in it. The grasp reflex, once elicited in the remainder of the hand, could be sustained by traction on the anæsthetic finger. Voluntary grasping of an object in the unanæsthetized fingers often became perpetuated as a grasp reflex, but voluntary grasping with the anæsthetic finger was always relaxed without difficulty. Though Hoffmann's sign was normally absent, a light stroke on the palmar surface of the digits at the same time as the stimulus for Hoffmann's sign was performed resulted in the appearance of a large brisk jerk in the stimulated and two neighbouring fingers, but not in the thumb. There was a mild grasp reflex in the toes of the left foot, but not of the right.

The grasp reflex could not be elicited from the centre of the palm of the left hand, but a stationary contact in this situation resulted in slow halting closure of the hand so that the fingers flexed to palpate the stimulating object and eventually grasped it. If the examiner's finger delivered the stimulus his finger was grasped at first lightly, but eventually very firmly for periods of about five to ten seconds. Any attempt to withdraw the stimulus resulted in an immediate and powerful tightening of the grip (trap reaction) which would then last some five to twenty seconds. This type of grasping could be obtained without any perceptible movement on the palmar skin. A rapidly moving stimulus either evoked a grasp reflex or no response at all. A stationary touch to the ulnar border of the hand was followed by an ulnar rotation of the hand made in a series of fumbling contacts with the stimulating object. The fingers progressively closed upon the object and after one or two palpating movements closed around it and grasped it, at first lightly, then more strongly. These reactions were constantly obtained whether they took place within the patient's field of vision or not. When her attention was drawn to them they ceased and she professed surprise that they were occurring. If the attempted withdrawal of the object had resulted in a strong grip she was unable to relax when asked to do so and would use the other hand in attempts to release the left. At a time when the stimulating object was contained in the fumbling left hand and any attempt to withdraw it resulted in a powerful grip (trap reaction) it was still possible to open the hand with ease by a passive pull on the flexed fingers, though the object still remained in the hand. Pressing the stimulus suddenly into the palm did not result in any sudden tightening, but movement of it in any other direction immediately and invariably did so.

If the fingers of the left hand were closing upon the stimulus when it was suddenly withdrawn the hand opened and advanced in the direction of withdrawal. If no further contact were made the hand slowly closed and came to rest after moving some 20 to 30 cm. If further contact were made and the stimulus further withdrawn a series of groping movements in the direction of contacts could be made and could be renewed intermittently for several minutes. If an interval of some ten seconds were allowed to elapse since the last pursuit a moving contact failed to elicit further pursuit unless the stimulus were first allowed to remain stationary long enough to evoke a further palpating and closing reaction. The direction of groping was only approximate but further contact was often secured when the stimulus had not moved more than 10 to 20 cm. With the exception of some visual phenomena which will be noted later, all the pheno-

mena of pursuit were obtained with equal ease whether the patient were blindfolded or not provided the eyes were not fixed on the hand. If she looked fixedly at the hand the responses usually did not occur but it was difficult to maintain her attention thus for long.

Case 8.—A man, aged 65 years, suffering from a progressive cerebral disease presumed to be a left frontal glioma, was attentive and co-operative but presented a generalized slowness and uncertainty in movement. His gait was slow with considerable hesitation before each small step. He had no defect in power of voluntary movement and no apraxia. Though slightly disoriented he recognized the examiners on successive days and could maintain a simple conversation. The right hand habitually grasped the bedclothes. The right arm showed a tendency to maintain imposed postures for a minute or longer whereas the left rapidly lapsed into resting posture. When the arms were outstretched in front of him a small irregular tremor of the fingers of the right hand, and in lesser degree of the left, was observed. His gaze was often fixed on some small object for minutes at a time but he would turn and look to the examiner without apparent difficulty when ordered to do so. At rest there was no consistent resistance to passive movement in any limb. The tendon-jerks were all very brisk in the right arm and leg, sluggish in the left arm, with moderate left knee-jerk and absent left ankle-jerk. Both plantar responses were flexor.

Instinctive sucking with turning of the head towards the stimulus was provoked with ease by a touch to the right side of the lips and the facial skin just below the right lower lip. The right side of both upper and lower lips pouted, and when they had surrounded the stimulating object the tongue protruded between the lips and also rhythmically contacted the stimulus. This was not evoked from the left side of the mouth. If the eyes were open and the stimulus approaching the lips was allowed to enter the patient's field of vision sucking movements commenced and the head turned to bring the stimulus nearer the lips when it was still 10 to 30 cm. distant from them. On one occasion the head turned well round to the left to bring the right side of the mouth nearer an object approaching in the left visual half-field. The whole evolution of these movements could occur while the patient's eyes turned to fix the approaching stimulus. There was no change in posture or behaviour of the hands during the manifestations of instinctive sucking.

An object introduced beyond the lips so as to make a moving contact with the right side of the alveolar margin of the jaws induced a biting movement, together with parting of the lips. At times the patient appeared unable to relax the biting movement for a few seconds ("bulldog phenomenon"). This phenomenon was present only on the one side.

This patient was examined on a number of occasions and the status of his grasping responses remained practically constant over a period of three weeks. At no time did he show any difficulty in performing or releasing simple willed movements. He used his hands naturally in eating, except for a slowness in total behaviour that has already been noted. A grasp reflex was regularly elicitable from the usual area of the right hand, both localized and total responses being obtained by firm moving pressure. They were not obtained by a moving brush stimulus. He could relax a fully developed grasp reflex only with great difficulty. A grasp reflex could also be obtained in the left hand but with less regularity and only by using a firm distally directed pressure over the first interphalangeal joint.

The instinctive grasp reaction was obtained with ease from the right hand, and in less developed form from the left hand. A touch of any part of the

palmar surface of the right hand, continued for two to five seconds, evoked a gentle closing of the fingers upon the stimulating object, a series of palpating, orienting movements in which the fingers and thumb surrounded the object comfortably, then gave several light grasps leading up to a final strong grip. Escape of the object during the preliminary movements led to a pursuit reaction, and further touches on any part of the hand to a magnet reaction. The magnet and groping reactions could be continued for periods of five minutes or more, and were of the same nature if the eyes were covered, or vision allowed but fixation and attention were maintained elsewhere. Groping towards an object that had suddenly entered his field of vision will be described later (Section V).

Once this type of grasping had been facilitated the right hand would turn to grasp a first contact on the back of the hand after an interval of more than a minute since the last grasp. If an object were enclosed within the hand and slight closing movements were in progress the slightest movement of the stimulating object out of the hand in any direction, whether the fingers were touched by the movement or not, induced a sudden and immediate grip (trap reaction) by the whole hand. The patient could immediately open the hand if told to do so during closing movements but if a firm grip or trap reaction had developed he could not relax the hand for a period of many seconds, and then only very gradually. This reaction was not evoked by strong pressure into the palm, even when associated with movement. The left hand was less responsive to touch and grasped usually only in response to prolonged touch within the palm. The trap reaction could then be strongly elicited in this hand. The magnet reaction was weak and brief.

A touch on the right foot elicited small alternating movements of flexion and extension of the toes of this foot against the stimulating object. No grasp ensued. When the foot was brought into his visual field and an object held near it the foot sometimes moved into contact with the object but no further movements were observed. No such responses were found in the left foot.

A number of observations were made on the right hand to attempt to learn more of the adequate stimulus for instinctive grasping. A light touch was most effective, after an interval without stimulation, when applied to the radial half of the palm, and particularly the distal aspect of the thenar eminence. After facilitation by previous grasping the movements of the hand produced by stimulation of this area were more ample and of briefer latency than from elsewhere. The whole palmar surfaces of the thumb and forefinger were the next most sensitive areas, and any part of the remainder of the hand was moderately sensitive. The dorsal and ventral surfaces of the wrist had a moderately high threshold. In the radial aspect of the palm, and over the thumb and forefinger a touch with a few hairs (? 4 to 8) of a camel-hair brush could elicit the reaction. The palpating movements were very lightly performed, chiefly with the thumb and forefinger, and he seldom lost all contact with the object once it had become enclosed by the fingers.

If a small object (a 5 cent coin) were pressed firmly into any part of the palm of the outstretched hand and left there, no response occurred. If it were moved very slightly, either by the observer or by gravity, closing movements began and ended in an attempt to palpate the object. If during such movements the coin were pressed firmly into the palm, by means of a pencil which did not itself touch the hand, the movements immediately ceased and did not recur until further movement of the coin occurred. A large object was a more effective stimulus in the sense that the movements began, and progressed to a final grip, more rapidly. The effect of surface area of the object was tested by placing conical objects varying from a thin tapering brush handle to a heavy paper tube

2·5 cm. in diameter at one end and 5·0 cm. diameter at the other, in the patient's right hand. If the smaller end of the object were placed in the ulnar part of the palm the movements invariably were such as to bring this end to the radial palm and then to progress along the object to reach the larger end. If the larger end were placed in the ulnar part of the palm, this end of the object was brought into the radial part of the palm when it was palpated and grasped without any attempt to palpate the other, smaller end. The thumb and forefinger always led the palpating movements. If the conical rod was placed squarely across the palm with the larger diameter to the radial side the grasping usually progressed along the object to reach its larger end. All these observations suggested that the reaction progressed towards greater surface area. But if the conical rod was placed across the palm with the smaller diameter towards the radial side irregular movements up and down the object began, as if there were a conflict between reaching the radial end of the object and the larger ulnar end.

On another occasion strips of adhesive tape were attached along the palmar surface of each of the four fingers. A pull on the adhesive tape when the fingers had been previously either passively flexed or voluntarily flexed did not evoke either a grasp reflex or instinctive grasping. If a grasp reflex was elicited in the usual manner a pull on the tapes could then alone sustain the response for one to five seconds. If the same pull on the tapes was made during the closing phase of an instinctive grasp reaction the fingers were easily extended and no new flexion was elicited. The trap reaction could not be elicited by pulling on the tapes, and when the trap reaction was elicited by movement of the stimulus a pull on the tapes was resisted but added nothing to the reaction. The instinctive grasp reaction could be elicited by a changing light contact on skin covered by adhesive tape.

This patient was seen again one month later, when a complete right hemiplegia with aphasia had developed. No grasp reflex or instinctive grasping was now obtainable in the right hand, but both were obtainable in the left as before. No sucking or biting could now be obtained on the right side, but both were obtained from the left side of the mouth. Neurosurgical exploration was refused.

Case 1.—A. B., whose strong grasp reflex in the left hand has already been analysed (p. 117), showed a weak instinctive grasp reaction and rarely a visual groping. When walking he used either to grip his coat or keep his fingers stiffly extended. He usually slept with the left hand gripping the blanket.

In this patient there was usually no response when an object was placed in the resting palm or when a localized (stationary) contact was made on the palmar aspect of the fingers. On a few occasions, however, the fingers flexed very slowly in response to such a stimulus and could be voluntarily relaxed with ease if no stretch of flexors had occurred. When the stimulus escaped between the left thumb and the index finger as such a grasp was developing, the fingers extended and the hand sometimes moved so as to follow the escaped stimulus for several cm. This fragmentary "magnet" reaction occurred only in a direction radiating distally from the thumb and first two or three fingers. Another type of projection of grasping, also described in one case by Adie and Critchley, was seen when Case 1 actively pulled with the normal right hand on the flexed fingers of the observer. The left hand then almost invariably moved to grasp the observer's wrist.

Such minimal, fragmentary, instinctive reactions appeared in this patient only on days when the grasp reflex was very strong, and were then avoided by the patient only with difficulty and intense concentration.

The basic reaction by which "the instinctive grasp reaction" is identified was the fairly regularly elicited closure of all fingers and thumb around an object which had produced a stationary light touching contact with the radial side of the palm. This was present in all the 19 cases we have investigated. In every case the response was intensified by suddenly moving the object as to withdraw it (trap reaction) but this and a "final grip" was not necessarily obtained at every examination. The magnet reaction was obtained in some degree at some time in every patient, but pursuit of repeated touches and instinctive groping were found only in approximately one-third of the patients. The magnet reaction or groping were not found without the closing reaction.

Most of the patients who showed the instinctive grasp reaction were mentally confused. They were usually restless. The instinctive grasping reaction was never observed when the arm was totally paralysed for voluntary movement. Even if consciousness was severely impaired, the character of the closing, final grip and trap phases of the instinctive grasp reaction was the same as described in co-operative patients, such as Cases 6, 7, and 8, mentioned above, and fragmentary magnet reactions could often be obtained.

(*ii*) *The Motor Response of Instinctive Grasping.*

The motor response was a movement such as to bring the stimulating object toward the radial part of the hollow of the palm, and therefore varied according to the area of the hand stimulated. If the radial part of the palm was first touched, only an irregular, halting closure of the four fingers and the thumb occurred. If, however, the palmar surface of one or more of the fingers was touched, the touched fingers began small grasping movements usually assisted by the thumb. The alternating flexions and extensions of the digits were such as to embrace a little more of the object in each phase. There was thus a movement of the whole hand toward the object. In a succession of such movements the patient's fingers climbed up the observer's stimulating finger. The brief movements of extension of the wrist and forearm to accomplish this approximation to the stimulus were, like those of the digits, irregularly and weakly performed. Whether elicited from the palm or from the fingers the response was an alternation of flexion and extension. The first movement appeared often to be flexion, but the movements begin so gradually that a small extension could pass unnoticed. The progressive nature of the series of contacts was as much due to movement forward of the finger in the extension phase as to pulling on the object in the flexion phase.

If the contact were made in the cleft between two digits abduction and adduction alternated with the flexion-extension movement.

When the stimulating object had been brought into relation with the hollow of the palm, all the digits closed upon it, still palpating it lightly, in a series of closing reactions. A tightening, the final grip, then usually occurred, often preceded by one or two lesser grasps. The tightened grip could last for several seconds, and when spontaneously released it would often be repeated before fading. An irregular fluctuation therefore characterized the reaction from beginning to end.

If the back of the hand was the part first touched the whole hand turned to the stimulating object, or so moved round the object as to bring it to the palmar aspect. This was accomplished slowly in a series of small movements, each of which established fresh contact nearer the palm. A first contact with the ulnar or radial border of the hand determined a corresponding half rotation.

We were not able to observe any difference between the movements of adjustment of the whole hand, which entailed movements of the wrist and forearm, and the simpler flexion and extensions which performed simple palpation. All were weak, irregular, and frequently tremulous. The movements of pursuit were of the same character. The first movement was commonly a small extension of the fingers but flexion followed immediately. If the stimulus was pulled away from the flexing fingers the next phase was a wider extension with more active projection of the whole hand, so that the "magnet reaction" had the character of an exaggerated extensor phase of the alternating movement followed by flexion. The co-ordination of movement was only approximately directed, so that effectiveness was secured by the fumbling succession of small movements, maintaining some contact with the stimulus, and not by one perfect act.

Electromyographic studies of the instinctive grasp reaction showed that the response, like that of the grasp reflex, was usually clonic (figs. 9B and 9C). The preliminary movements were accompanied by fleeting, often grouped bursts of impulses (figs. 9A and 10A) alternating in flexors and extensors as the hand opened and closed. The discharge leading up to the grip gained momentum only very gradually and this distinguished it clearly from the grasp reflex. The extensors and flexors of the wrist maintained an appropriate postural reaction, not differing from normal voluntary movement of the same intensity. As a strong grasp developed fixation of the wrist-joint occurred.

The "trap" phenomenon, elicited by a sudden pull on the finger

flexors when a closing reaction was already established, constantly manifested a strong gripping contraction. The electromyogram often showed a corresponding enhancement of clonic beating in the rhythm of discharge when this occurred (fig. 9D). The enhancement obtained in this way was, however, maintained for some seconds after the pull on the flexors ceased, whereas in the grasp reflex it was more strictly proportional to the intensity of proprioceptive stimulation. If the extensor muscles of the wrist were taking part they continued their contraction throughout (fig. 9D). The electromyogram of a fully developed trap reaction differed in no constant way from a fully developed grasp reflex, both differing from voluntary contraction only in irregularity of discharge. Clonic tremor was, as in the grasp reflex, related partly to the suddenness of the passive pull on the hand, and partly to the general liability of the affected limb to tremor. The sudden tightening which sometimes occurred as the stimulus entered the hand had the same characteristics (fig. 9B). If the trap reaction was elicited only by a sudden lifting of the stimulus from the palm of the hand when the fingers had lightly surrounded the object, and pull on the fingers was thus avoided, clonic grouping of discharge was minimal or absent (fig. 10C). Similarly, a "final grip," or less powerful grasps preceding this, often showed steadily maintained types of electrical discharge (fig. 10D).

The reaction to sudden movement of the stimulus during an early closing reaction when only the tips of the fingers surrounded the stimulus differed from a fully developed trap reaction only in its brevity (fig. 10E). This figure also shows the rapid rhythmical alternation of flexion and extension as the object was escaping the grasp.

In groping the extension of the fingers on contact was more obviously the immediate reaction, and if the stimulus was brief the flexor contraction was delayed by as much as 0·2 second (fig. 10F).

Electromyographic studies therefore document the slow development and weak nature of the movements of the closing reactions, and the powerful and rapid reinforcement which developed either gradually as the full grasping area of the hand enclosed the object, or more rapidly if the stimulus tended to escape.

(iii) The Adequate Stimulus for Instinctive Grasping.

The most effective stimulus was a light stationary touch on the skin, using an object that is not too small, e.g. the end of the examiner's finger. Contact over an area less than about 25 sq. mm. was usually ineffective. When responses had been facilitated by a succession of reactions further

responses could be obtained by contact with as little as five or six hairs of a camel-hair brush. The larger the area stimulated the more easily was the response obtained, and if successive responses succeeded in establishing greater and greater area of contact the grasps became perceptibly stronger. The final strong grasp, though not shortened in latency, might thus be regarded as the ultimate maximal response to maximal area of contact. The latency between stimulus and first response was often several seconds. A new stimulus was much more effective just after a closing reaction. Even when facilitated the closing of the hand often developed very slowly (fig. 10A). It was easier to provoke the response to touch by intermittent contact. Movement of the stimulus did not facilitate the response, though it could modify it (magnet reaction) when once developed. Pull on the skin in any direction by means of adhesive tape attached to the skin could not evoke the reaction. The reaction seemed in most patients to be more difficult to provoke when the patient's attention was given to the examination. In some confused patients the reverse was found. The most effective method was for the examiner to lay two fingers in the radial part of the hollow of the palm, between the thumb and the forefinger.

The complex adjusting movements resulting from stimulation of the dorsum or side of the hand required precisely the same stimulus as did the more simple closing reactions. Heavier pressure appeared to inhibit all these reactions, but increase in area of light contact certainly facilitated them. That the finger movements themselves provided a serial stimulation was seen by the cessation of movements if the stimulus was withdrawn following a contact. The movements each provided a light pressure contact, and if one of the movements provided a tight squeeze (heavy pressure) there was usually a distinct pause before further movements were resumed (fig. 10D).

The reaction to attempted removal of the stimulus varied according to the stage of instinctive grasping that had been reached. If no closure reaction had occurred within the previous two to five seconds a moving or changing stimulus was usually without effect (except for the possibility that it might elicit a grasp reflex). If a closure reaction was in progress, or had just ceased, movement of the stimulus, whether a simple removal or a change in the light contact, determined a further response. The nature of the response varied according to the area stimulated, and the posture of the hand. A slow withdrawal of the stimulus merely intensified any reaction in progress so that the most simple form of magnet reaction maintained continuous contact with a retreating stimulus. If the touch

had been on the dorsal or lateral surface of a finger the hand and forearm would sometimes follow the contact without movement of the fingers, which began when a broader contact was obtained. If the movement were such as to escape from further contact with the fingers the magnet reaction and eventually groping could be made to appear. A fresh stimulus on the dorsum of the hand shortly after a closing reaction evoked pursuit of further contact. If the stimulating object was already enfolded by the fingers a sudden tightening of the grip (trap reaction) almost constantly developed.

In the magnet reaction the patient's hand after a brief latency made movements to maintain contact with the preceding tactile stimulus, approximately in the direction it was withdrawn. The magnet reaction could be most readily elicited if the removal of stimulus was relatively slowly performed and moved distally in the axis of the limb. It was usually not found unless a closure reaction had already been elicited within about ten seconds.

The area of further contact which prolonged a magnet reaction could be very small, e.g. the tip of the observer's finger. One patient followed a contact with a camel-hair brush. In attempting to define the part played by movement of the stimulus we found that, when the eyes of the patient were covered, he could still follow a retreating series of contacts even though the examiner made each contact with a moving touch in a direction contrary to that of withdrawal. Thus the projected movement of the hand was invariably made more in a direction corresponding to the part of the hand stimulated and not in the direction of the movement of stimulus. The direction of pursuit was roughly in a line vertical to the skin at the point touched. Electromyographic studies with a sensitive pressure recorder (figs. 10A, 10B, and 10F) indicated that the release of pressure has to be considered an important factor, for movement immediately followed removal of a brief stimulus, and fluctuation in pressure was difficult to avoid. If a simple contact were prolonged an adjusting movement preliminary to closure ultimately began. Since it was not possible to maintain an absolutely constant contact pressure this movement could also be obtained from the dorsum of a finger without removing the stimulus completely.

If the observer attempted to remove the object in any direction after it had become enfolded by a closing reaction, a sudden tightening of the grip (trap reaction) was almost constantly obtained. This tightening also appeared when the stimulus was suddenly moved further into the patient's palm, and was developed before any pull or displacement of the flexed

fingers occurred. It was not elicited by a simple increase of pressure against the skin, either of the palm or of the flexed fingers. A drag on the skin of the fingers in any direction by means of adhesive tape attached to them failed to cause this tightening to develop during a closing reaction. Any or all of the fingers could thus be passively extended with an ease that was proportionate to the degree of closing reaction that was proceeding at the moment of pull. If some small flexion movement was in progress it slowed this passive extension of the fingers slightly, but rapidly subsided. No fresh flexion was set up by the traction. If on the other hand the stimulating object in the hand moved just before traction was made on the adhesive tape a powerful effort was necessary to overcome the resulting finger flexion of the resulting trap reaction. There was no evidence that stretch of the flexor muscles entered into this reaction. The movement of escape appeared to be the essential factor, and was resolved into a sudden change of contact, probably simple lessening, over a wide area of palmar surface of the hand and fingers.

We therefore concluded that, just as positive contacts of increasing area determined increasing closing responses, lessening of contact led to some reinforcing factor. Of this reinforcing factor it can only be added that a preliminary closing response was usually necessary before it could be clearly elicited, whether it occurred as a magnet reaction, or as a trap reaction to an already enfolded stimulus.

Since tactile sensation has a high rate of adaptation it is possible that all phases of the closing reaction are determined by changes in tactile pressure. The instinctive grasp reaction is fundamentally a progressive series of grasping movements, the most simple being an extension, followed by flexion, of the digits, wrist and elbow. The extension movement which brings the palm of the hand closer to the stimulus before the next grasping appears to be stimulated by light tactile contact. The first movement leads to lessening of pressure which in turn stimulates the next flexion.

(iv) The Relationship between the Instinctive Grasp Reaction, the Grasp Reflex, and Other Reflexes.

It has been mentioned that not all of the patients with a strong grasp reflex had instinctive grasping and groping. When the latter was well developed, we more often found a certain degree of grasp reflex, but not always. A strong grasp reflex was found in several patients without any response to stationary touch, or groping, and this was clearly demonstrated in three hemiplegic patients with well-developed grasp reflex in the para-

lytic hand. In 3 cases the instinctive grasp reaction was well developed without the grasp reflex. The following cases illustrate the variability of the relationship of the strength of the instinctive grasp reaction and the grasp reflex.

Case 9.—A 14-year-old boy with cerebral abscess, secondary to sinusitis. There was a moderate degree of left hemiparesis. The first day of examination, he was alert and could read a newspaper. Touching the palm of the hand, without movement, elicited a closing reaction, followed by a stronger grip, in either right or left hand. There was no response to moving contact over the areas for elicitation of the grasp reflex in either hand. The following day he was stuporous and not co-operative yet the simple closure with final grip could be elicited on both sides. In the left hand a magnet reaction was elicited also. The grasp reflex could not be elicited in the left hand but was then present in weak degree in the right hand.

Case 10.—J. D., aged 75, had a left-sided spastic hemiparesis from cerebrovascular disease. A strong grasp reflex could be easily elicited on the right nonparetic side, but the instinctive grasp reaction was seen only as a weak finger closure when touching the palmar side of the thumb and the forefinger. This patient could co-operate but was mildly confused.

Case 11.—D. H., a 46-year-old woman with general paresis, was in deep semicoma and showed no response to verbal demand. The right arm was paralytic and no grasping phenomena could be provoked on this side. The first, second and third day of examination distinct instinctive closure, grasping, and groping were present on the left side but a grasp reflex could be elicited only on the second examination. In her groping movements the precision with which the hand turned around to grasp when the dorsal side was touched was remarkable. Her gaze was never directed towards the touching object.

Thus many patients presented both phenomena, the grasp reflex and the instinctive grasp reaction, as we have described them, especially if one of them was very strong. It was sometimes difficult to separate the two reactions when both were well developed. A distally moving contact on the palmar aspect of the joints of the fingers should however immediately elicit localized flexion if the grasp reflex is present. The closure of all the fingers with movements of adjustment in response to a stationary pressure in the palm establish the instinctive reaction. Movements of pursuit of a retreating object are also a reliable indicator that automatic grasping is present. When both reactions are present they appeared each to facilitate the other, for either could be elicited with greater ease just after the other, but during a grasp reflex in one or two fingers it was not possible to stimulate a closure of the others. Localized contact with the dorsum of the hand inhibited the grasp reflex and may initiate the instinctive reaction.

The positive correlation of the instinctive grasp reaction with instinctive sucking and Mayer's sign, and its lack of relation to changes in tendon reflexes, the presence of an extensor plantar response, or with spasticity was approximately the same as for the grasp reflex. Since the two condi-

tions so frequently occurred together this general relationship to other signs was to be expected. The instinctive grasp reaction, like the grasp reflex, was not influenced in any way by the position of the body or head. Since the relationship between instinctive grasping and reflex sucking is of special interest it may be stated that in 10 patients with the instinctive grasp reaction reflex sucking was strongly developed in 5, in 2 only a trace of sucking response could be obtained, and in the remaining 3 none at all. In one patient an instinctive grasp reaction was present without either grasp reflex or sucking response.

In conclusion the instinctive grasp reaction was found to be a progressive series of movements which on analysis differ both in type and in adequate stimulus from the less variable and adaptable phenomena of the grasp reflex. The chief clinical differences which distinguished instinctive grasping were the essentially tactile nature of the stimulus, the wide area over which it was effective, the complex nature of the initial closing movements, their long latency and intermittent progressive course, and the reinforcing effect of sudden lessening of contact. Though the two types of response are frequently associated there was no evidence that one was an enhanced form, or even a modification, of the other. Their relationship was that of two entirely different nervous mechanisms using the same effector mechanism.

(v) The Effect of Vision on the Instinctive Grasp Reaction.

The reactions we have described as the "instinctive grasp reaction" have a series of adjusting movements as an essential preliminary. Such movements could be simple or complex. If an unsuccessful or partial grasping movement had just been elicited the hand pursued the escaped object. In general we were not able to observe any difference in these reactions if the grasp and pursuit took place in the patient's field of vision or if he were blindfolded. In a few cases, if the patient were allowed to look at his hand all grasping phenomena might be suppressed within the limits that he could prevent the reaction. We suspect that this was the negative aspect of the greater ease of eliciting the phenomenon if the attention of the patient were distracted.

That objects in the periphery of the visual field were of positive significance was suggested by the following observation.

In Case 7, a patient whose instinctive grasp reaction has already been described in some detail, a visual phenomenon was observed at our first examination, but not at our second or third (three and five days later, when her condition had deteriorated). When a magnet reaction or in-

stinctive groping had been elicited in the left hand and had subsided without further contact, introduction of the stimulus (observer's hand) into the left half of the patient's field of vision caused a movement of the patient's left hand toward it, and further pursuit. This reaction was most convincingly observed when the interval after the previous grasp was less than ten seconds, and the stimulus moved slowly towards the hand of the patient, which then arose to meet it when the two were about two to three feet apart. This reaction occurred on four or five occasions. On a great many other attempts no reaction occurred. The positive reactions were all in the left visual field. The patient did not look directly at the stimulus, and indeed seemed unaware of its presence, being at the time engaged in conversation and looking fixedly at the face of the examiner. In the days after the operation all grasping phenomena disappeared, but as the voluntary contraction returned the grasp reflex and instinctive grasp reaction to touch both reappeared, but both were now difficult to elicit regularly and the reaction to visual stimuli no longer occurred. The patient was fully co-operative in all these examinations, and we satisfied ourselves that the grasping phenomena developed without her awareness, when her attention and visual fixation were held in some other direction.

In another patient, suffering from hemiplegic weakness from a fronto-parietal gunshot wound, reintroduction of the moving stimulus into any part of the half-field of vision on the same side as the grasp reaction as far as 100 cm. from the hand induced a movement of the hand to meet the stimulus. On two occasions this happened twenty seconds after the last tactile closing reaction. It was never elicited from the opposite half-field. There was no fixation of the stimulus by the eyes, the patient's attention being distracted elsewhere during the observation. A severe aphasia in this patient made it difficult to study the phenomenon more intensively.

In *Case* 8, already described above, instinctive grasping was present in both hands but was particularly well developed in the right hand. On several occasions, as long as one minute having elapsed after a grasp or closing reaction in the right hand, the hand would rise to meet the observer's hand if it were introduced into any part of the right half-field of vision. The hand reached towards the observer's fingers and began closing movements. This happened once in many trials when the observer's hand was introduced in the patient's left-half field of vision. At other times there was either no reaction on the left or the left hand would begin fumbling. The patient was attentive and co-operative, but was mildly confused. He used his hands without difficulty in eating food. The right arm would maintain for some minutes a catatonic attitude imposed upon it, and would imitate such movements as the examiner made (waving the hand, opening and closing the hand, &c.) even though the patient's visual fixation was directed elsewhere. Any movement in the field of vision strongly attracted his visual fixation. The examiner, during visual groping, had to reinforce the command which maintained the patient's visual fixation elsewhere.

Case 1, who was mentally alert and co-operative, was noted on several occasions to move his left hand towards an object in the observer's hand. When questioned he stated, "I want to have it because it is in front of me." After a time the left hand grasped an object that had been lying close to it. He was unable to explain this action. If he decided not to take hold of this object he could avoid grasping it until he again forgot himself.

These observations and our impressions gained from similar chance observations before we began the present investigation indicate that in the patient who is mentally alert vision may project the cutaneous stimulus of instinctive grasping both in time and space. More precise observation must await more suitable material.

(*vi*) *Prevention and Release of The Instinctive Grasp Reaction.*

Patients who could co-operate in examination appeared to avoid the instinctive grasp reaction if they could give their attention to it, but the reaction reappeared in spite of this instruction if they were engaged in conversation or otherwise distracted. Confused patients would begin to grasp the examiner's fingers even while attempting to avoid further examination.

A co-operative patient could cease the closing reaction immediately if requested to do so. He often seemed unaware that it was in progress, and manifested surprise when told to cease. If a final grip had developed it could be relaxed after a little delay. If the observer tried to withdraw the stimulus and thus elicited a trap reaction the patient had great difficulty in releasing the grasp which could persist for many minutes under these circumstances. The same patient would have no difficulty in opening and closing the empty hand, or even if an object were placed in the palm. Delay in release of a fixed object such as a door handle following a purely voluntary grasping was related usually to the presence of a strong grasp reflex and involuntary pull upon the object.

The patient always appeared able to control instinctive grasping with greater facility than he could a grasp reflex of corresponding strength. Fluctuation of attention may therefore explain the greater variability of the instinctive grasp reaction.

V. General Discussion.

The abnormal grasping phenomena which appear in patients suffering from cerebral lesions have been subjected to a clinical analysis which, beginning with the more constant and less adaptable type of response (grasp reflex), appears to give some insight into its physiological mechanism, and leads to more clear definition of the more complicated variations ("instinctive grasp reaction").

Grasping is a complex movement in which flexion of the fingers and thumb, adduction of any or all of these, and opposition of the thumb may be found in various combinations so as to prevent escape of an object from within the orbit of the hand. Fixation of the wrist and elbow joints is an accessory part of the process. Whether opposition of the thumb is a *sine qua non* of the grasp appears to us to depend upon the size and the nature of the object that is grasped. A twig may be grasped by flexion of any single finger alone, a ball obviously cannot, and needs assistance from the thumb.

Our analysis indicates that two different types of grasping reaction are commonly observed as signs of cerebral lesions in man. One, the grasp reflex, is a flexion and (or) adduction of one or more digits, with opposition of the thumb and flexion of wrist and elbow as secondary and modifiable characteristics. This response is chiefly elicited by, and opposes, traction on the flexed digits, and we may therefore assume that the type of grasping is that which is generally concerned with counter-traction. If there be further purpose such as righting of body posture it was not evident in our investigation. The second type is a more complex and complete response to contact of the hand with an object, the instinctive grasp reaction, with accessory movements of adjustment and pursuit. The end-result of this reaction is an enfolding of the stimulating object and prevention of its escape.

We do not feel it necessary here to enter further into discussion of the propriety of inclusion of flexion of one or more fingers, in the absence of movement of the thumb, as legitimate fractions of a "grasp." Movement of the wrist, elbow or shoulder may at times be the leading feature of the instinctive grasp reaction. The total act of grasp or prehension is nevertheless unmistakable. The same general consideration allows flexion movement of one or more prehensile toes within this physiologically determined definition.

The grasp reflex: It was found that the most stereotyped and simple form of pathological grasping as is commonly elicited by the classical method of drawing two fingers out between the index finger and thumb of the patient, could be broken down into a group of partial responses by appropriate stimulation. The most important of these partial reactions was flexion of a metacarpo-phalangeal or interphalangeal joint of any digit (including the thumb) in response to a contact moving distally on the skin of the palmar aspect of the joint concerned. A contact with the skin bordering the space between two digits, moving ventro-dorsally, elicited adduction of the two digits concerned. A distally moving contact over

the middle of the most proximal part of the palm elicited flexion of the wrist. As the stimulus was increased in intensity the resulting contraction spread to include flexion of the neighbouring joints. In each such local contraction, or in any combination, the first phase of the reaction (the "catching phase") was brief, and developed little power of contraction, but possessed the property of enabling a powerful response to tension on the contracting flexor or adductor muscle concerned (the second or "holding" phase). Both the fractionation of the response and its trigger mechanism have been found in a large number of patients, and can readily be verified by simple clinical means.

The adequate stimulus for this response, which we believe is the true grasp reflex, was therefore resolved into two components, that of the initial catching phase, and that of the reinforcement in the second or holding phase. It was shown that the adequate and essential stimulus for the catching phase whether in one joint or in many, was a distally moving pressure contact which may be little more than light touch when the reflex was very active. When the reflex was difficult to elicit firm and deeper pressure was necessary, but this still had to be performed in a distal direction. Drag of the skin with the stimulating object gave sufficient of the movement factor to be effective, without actual movement of the object along the skin surface. Traction on the skin by adhesive tape attached to it was ineffective. Complete anæsthesia of one finger abolished the response in that finger, but as long as any deep sensation remained the response was obtainable. The directional characteristic of the adequate stimulus evidently requires a serial stimulation of deep-pressure receptors. The full receptive field for the reflex was constantly a crescentic area such as to include the palmar aspects of all the metacarpo-phalangeal and interphalangeal joints, with a small proximal extension along the thenar eminence to include the palmar aspect of the wrist. It extends a short distance dorsally over the web of skin between any two fingers, and does not include the centre of the palm, the hypothenar eminence, the tips of the fingers, or any part of the dorsum of the hand. The general outline of the area is shown in broken line in fig. 1. The most sensitive portion, or focus, of the receptive field is the skin covering the palmar aspect of the proximal interphalangeal joints.

The holding phase of the grasp reflex was found to be the result of reinforcement of the contraction produced in the first phase by a pull on the contracting muscles. Passive stretch of the muscles would not alone elicit the grasp reflex, even if a sudden pull were made on adhesive tape attached to the palmar aspect of the passively flexed fingers. Neither

slight voluntary contraction, nor spastic myotatic reflex could substitute for the catching phase, the preliminary trigger response, produced by moving pressure contact. The proprioceptive, holding phase of the grasp reflex differed from the simple stretch response in spastic finger flexors in occurring at a variety of initial lengths of the muscles, in adapting itself to the joint over which the stimulation occurred, and in its lack of correlation with the state of the resting tendon reflex of the fingers. The grasp reflex could be elicited as the wrist was concurrently being passively flexed, thus lengthening the flexor muscles. In contrast to spasticity and the tendon-jerks, the grasp reflex was abolished by complete anæsthesia of the stimulated finger. Once a catching phase had been evoked and reinforced in another finger the anæsthetic finger flexed, and the response in it, and to a lesser degree in neighbouring fingers, could then be maintained by continued traction of the anæsthetic finger. The stimulus for the proprioceptive phase is undoubtedly stretch, an increment of passive tension, acting on a centre already facilitated by deep cutaneous receptors.

In view of the lightness of contacts adequate to stimulate the catching phase when a well-developed reflex had been facilitated by repetition we consider it unlikely that nerve endings in periarticular structures are necessarily involved. The firm pressure that is required when the reflex is difficult to obtain, and the situation of the focus of the receptive field over the first interphalangeal joint have doubtless given many the impression that passive pull on the fingers is alone sufficient. The brevity of the catching phase under these circumstances further requires an immediate stretch of the flexors if the reflex is to be developed. Nevertheless anæsthesia of the finger abolished this response.

The pathological grasp reflex was characterized more by the difficulty with which the patient could prevent or release the response than by the power of sustained contraction once it was evoked. A high threshold but nevertheless powerful contraction could be found in many normal subjects. The most constant response in our patients was a flexion of all four fingers when stimulated by a firm pressure of the observer's fingers moving distally from the centre of the palm. Several of the local reactions were thus elicited at the same time. If a firm locking was to be obtained an acceleration of the stimulus and an increase of pressure was necessary as soon as the response began. This type of response was regularly present in many patients in whom grasping in response to the more conventional method of drawing the stimulus out between thumb and first finger was weakly developed or entirely absent. The same means of stimulation will often elicit a grasp reflex in the toes on the same side as the affected

hand. The reflex in the foot was rarely more fully developed than in the hand.

A combination of cutaneous and proprioceptive stimulation to secure a specific response is not unknown in the physiology of the nervous system. It was demonstrated in the limbs of the experimental animal by Magnus (1926) as the adequate stimulus for the "positive supporting reaction," by which contact of the sole of the foot with the ground transformed the plastic posture of the limb into that of a supporting pillar. The unusual feature of the grasp reflex is the cutaneous conditioning of a proprioceptive response which may then be kept up by stretch alone. In this respect its closest physiological counterpart is the extensor thrust reflex of the spinal animal. The peculiar properties of the stimulation adequate for the extensor thrust (or "direct extension reflex") include a momentary moving contact with the pad of the foot of the spinal dog, combined with concurrent and continued stretch of the extensor muscles of the limb, as early described by Sherrington (1903, 1910). Thus a complex integration of cutaneous and proprioceptive mechanisms can exist even as a spinal reflex.

The grasp reflex has, in its full development, a specificity of stimulus and a predictability of pattern comparable to other so-called "superficial reflexes" such as the plantar response and the abdominal reflex. It falls into the same general class as these, and shares with them a relationship to cortical mechanisms. In fully conscious patients, modification related to varying degrees of the patient's attention is however greater in the grasp reflex. We have satisfied ourselves that the basic response does not require conscious participation of the will of the patient. That under other circumstances the reaction is modifiable or preventable by the intention of the patient does not alter this evidence of its fundamental character. There is good evidence that it is inborn and stereotyped, for the grasping of the infant betrays the same characteristics we have described for the clinical sign in adults. Its gradual disappearance in infancy and the retention of some degree of the response in some otherwise normal adults indicates a process of control which is acquired slowly in the course of development and long after the development of power of consciously directed movement. Whether it falls within the category of reflexes or of instinctive reactions depends upon the definition of these terms. Walshe and Robertson (1933) objected to the use of the term "grasp reflex" and regarded it as but an aspect of a proprioceptive reaction in the whole musculature, "tonic innervation." The response was, however, present under circumstances where volition was completely excluded, and the other manifestations of "tonic innervation" as originally described by

Wilson and Walshe (1914) were not present. It is not a generalized disorder of the motor system as is spasticity. Our investigation revealed a specific stereotyped response to stimulation of the hand, developed in less degree in the foot, which reacts to an escaping pressure by prehensile flexion of the digits. We therefore accept the term grasp reflex.

The observations of Fulton (1934) and Bieber and Fulton (1938) which convinced these authors that the grasp reflex in monkeys is only a proprioceptive reaction were of two different kinds. Their finding that the grasp reflex was not abolished by infiltration of the wrist with local anæsthetic is open to the same objection as to the clinical experiment of Walshe and Hunt (1936), namely that deep pressure sensation is difficult to abolish in this way. That the grasp reflex should persist following deafferentation of the upper limb (Fulton), then being elicited by traction on the shoulder, is difficult to discuss in the absence of description of reaction to traction in the shoulder without stimulus to the hand, before deafferenting. When these authors further describe grasping and limb postures when the animal falls through space, the limb and shoulder being both deafferented, we believe a phenomenon different from the grasp reflex was certainly present.

The observations of one of us (D. D-B.) on the paresis of the hand in monkeys following cortical excisions lead us to the conclusion that in the earliest days following complete excision of area 4, when paralysis of the hand appears to be complete, a strong emotional stimulus, whether accompanied by falling or not, can lead to grasping of the hand and wrist. Under sufficient provocation the limb will be used in climbing. Under less exigent circumstances the fingers flex moderately slowly for many seconds. This reaction has no relation to stimulation of the hand. We find no reason to identify it with the grasp reflex, and regard it as a pattern of total reaction similar to the clawing of the thalamic cat when disturbed. We would provisionally class these reactions of the hand to traction on the shoulder and to falling described by Bieber and Fulton with this generalized type of reaction.

Fulton and his associates (1934) reported the grasp reflex to be more intense or only present when the patient lay on one side with the affected limb uppermost. This did not occur in either phase of the grasp in our material. In our experience with patients exhibiting positive Magnus-de Kleyn reflexes (but not a grasp reflex) the curling of the fingers due to increase in spasticity when the affected limb is uppermost may account for the change observed by others. The observation of Wechsler *et al.* (1936) in their first patient, that only the response to pull on the flexor tendons

of the fingers was increased by change of the body posture, without an effect on a grasp elicited by tactile stimulation, also suggests to us that spasticity was present. In animals with combined areas 4 and 6 lesions it should also be difficult to separate a true grasp reflex from spasticity, and to eliminate the effects of the righting reflexes on the latter.

The flexion of the digits of the hand and foot in response to light touch or pressure on the "interdigital pad," described by Marion Hines (1942) in her studies of grasping in the fœtal and macaque monkey, appears to correspond to the simplest type of our "instinctive grasp response." It was intensified by stretch of the flexed fingers, but this possibly indicates coincidence of the grasp reflex, for as in the human infant, the purely cutaneous response disappeared early in infancy, leaving for a time only a response to pull on the flexors of the fingers. We assume that the latter response was the grasp reflex. In discussing the significance of these responses Hines states (1942, p. 201) that the response to tactile stimulus alone was found in adult monkeys after excision of area 6. She goes on to state that following lesions of areas 4 and 6 in the cortex of adult monkeys there was no response to pressure or touch on any surface of the hand, but only to stretch of previously contracted fingers. On cessation of stretch the flexors relaxed. Such a response may also be complicated by spasticity, for in adult monkeys following area 4 lesions we ourselves found present for a time a resistance in the finger flexors that we would call spasticity by reason of its occurrence at a fairly constant length of the muscles and speed of passive extension, and its association with more obvious finger-jerks.

We therefore maintain that experimental investigation of the grasp reflex in animals requires re-examination, in terms of the definition of stimulus and reaction as proposed by us, before conclusions can be clearly defined as to its anatomical mechanism. Careful attention to the method of elicitation of the grasp reflex in the clinic also greatly increases its sensitivity and value as a physical sign of disease.

The instinctive grasp reaction: Most patients exhibiting strong pathological grasping phenomena show, besides the grasp reflex, a type of response that is manifestly more adaptable, and less stereotyped or predictable. Our investigation showed that the basic reaction was essentially an automatic response to a cutaneous stimulus, but capable of development into pursuit and groping in space, and we include all these manifestations under the term "instinctive grasp reaction." Many of the phenomena of this reaction were included in the "forced grasping" of Schuster, and of Adie and Critchley, some under their "forced groping." Not

only were features of the grasp reflex also included in the former term, but the reaction is in no sense "forced," being on the contrary a complex movement developed slowly and progressively in response to a highly specific stimulus.

The instinctive grasp reaction was found to be fundamentally an active enfolding of the stimulating object by the hand, and was accomplished in a series of steps or preliminary adjustments, by which the hand engaged with, and closed around, the stimulating object. The adequate stimulus, as for the grasp reflex, was also contact, but of lighter kind, amounting often to light touch only, without the factor of movement. Indeed heavy contact depressed the reaction. The area of elicitation was wider than that for the grasp reflex and included the whole palmar and dorsal surfaces of the hand, sometimes the distal forearm. The most sensitive part, or focus, of this wide area was the radial side of the hollow of the palm. The response could in many be elicited from the tips of the fingers, and the sensitive area was not especially related to the finger-joints as in the grasp reflex.

The motor reaction was both delicate and highly integrated. Each movement of the fingers was such as to bring a further contact with the stimulus closer to the hollow of the palm of the hand. There was thus a series of separate responses ending, if successful, in a complete grasp by the whole hand. The more simple closing reaction to contacts in the palm were regularly obtained and predictable, and usually those elicited from the palmar surfaces of the fingers were evoked with ease. Responses from the ulnar border and the dorsal surface, entailing a more complex turning of the hand and forearm were of higher threshold and appeared usually only after facilitation by previous grasping. All these movements were weakly performed and intermittent, as if the further contact with the stimulus resulting from one closing movement led inevitably to a further adjusting movement, and this to repetition of the cycle, thus giving the performance its progressive character. The latency of any individual movement following contact was long, often as long as three to five seconds, differing remarkably from the first phase of the grasp reflex in this respect. The final stronger grip, which often spontaneously occurred after the stimulating object had been completely enfolded by the hand, was similarly delayed, often by an interval as long as ten seconds.

The only difference between the closing adjusting movements described above and those that comprised pursuit of a retreating stimulus (magnet reaction) was that the latter normally followed an initial closing reaction, and only when the reaction as a whole was strongly developed

could be initiated *de novo*. When the stimulus moved to escape during a closing reaction the magnet reaction followed immediately, and if it escaped instinctive groping would often begin. The longer the interval which had elapsed since the last closing reaction, the longer the delay before pursuit of a new contact outside the palm.

Once the stimulating object had been enfolded by the hand an immediate, rapid, and forceful grasp could almost invariably be induced by any sudden movement of the object in any direction out of the palm. The closure of the digits in this trap reaction did not differ from the final spontaneous grip after closing, except in its brief latency and sudden development.

All our patients with the instinctive grasp reaction showed a closing reaction when a stationary contact was made in the radial part of the palm of the affected hand, and a trap reaction could be elicited with fair regularity in each. A magnet reaction could be developed from a contact on the palmar surface of the fingers after previous grasping in even the mildest degree of the reaction, and under favourable conditions each such patient could develop a closing reaction to stimulation of parts of the dorsum of the hand. Each of these reactions have been observed by us in states of semi-coma where there was no evidence that the patient could possess awareness or initiate a so-called "willed movement." Continued pursuit of an intermittent stimulus, instinctive groping and facile reaction to stimulation of the dorsum of the hand were characteristic of a strongly developed instinctive grasp reaction and were rarely observed in semi-comatose states. They were, however, observed in patients who made no such movements on response to our stimulation of the other ("normal") limb. Finally the instinctive grasp reaction though variable, possessed a fundamental motor pattern, and a relative order of ease of elicitation of its components that was fairly uniform throughout all our case material. It clearly included phenomena called "volitional" by Walshe and Robertson (1933). We found no evidence that volition, even in the sense of the "least voluntary" and "most automatic" used by these authors, can underlie its occurrence.

We should make it clear that just as grasping without stimulation of the hand is not classified as either grasp reflex or instinctive grasp reaction, so spontaneous groping movements without stimulation of the hand have been found by us only in circumstances where perseveration of ideas or hallucinatory phenomena could not be excluded as providing independent motivation. Such groping is not part of the instinctive grasp reaction. Our essential criteria for a basic instinctive grasp reaction, such as may be

used as a physical sign in the clinic, can be formulated as a deliberate progressive closure of the hand by means of a sequence of light fluctuating movements most easily elicited by a stationary light contact on the radial side of the palm. The response should be relatively stereotyped, and elicitable only or chiefly when the attention of the patient is directed elsewhere. Sudden firm pressure on the palm should abolish the response. Magnet and trap reactions should be demonstrable in some degree. With such criteria the instinctive grasp reaction was found to be a sensitive sign of cerebral disorder.

The adequate stimulus for the instinctive reaction is stationary light touch. Our investigations excluded pain, pressure, traction, and stretch of tendons both from its initiation and its perpetuation. The factor of movement was difficult to exclude. A moving contact rarely succeeded in initiating a response. After facilitation a slowly moving contact could be successful but did not shorten the latency. Too rapid movement of the stimulus greatly lessened its effectiveness even under these circumstances. On the other hand, removal of an established contact was both an effective stimulus and shortened the latency of response. In this respect the slightest variation in the touch contact was more effective than a movement of several millimetres. The contact provided by the examiner's finger or by an object in his hand was found to be subject to considerable fluctuation in pressure. A small object carefully placed on the skin and held then by gravity usually did not evoke a response. It is probable that with our relatively crude clinical methods of stimulation the long latency was related to a delay before a summation of stimuli due to fluctuation in the contact stimulus occurred, and that variation in touch was the true stimulus. From this point of view the progressive nature of the reaction, and the essential continuity of closing, magnet, trap reactions and final spontaneous grip are reduced to the operation of the same stimulus factor. The more simple closing movements could be reduced to a series of flexions and extensions (with or without corresponding abductions and adductions) of which the extensor phase was stimulated by contact and the flexor phase by the lessening of pressure due to the preceding extension.

The type and extent of response was related to the area of contact. The resulting movement brought about was such as to bring the next contact with a stationary stimulus closer to the radial part of the palm, but at the same time brought more surface of the fingers and palm into contact with the object. Full grasping power resulted usually only when the contact was made with maximal area of the palmar skin. The grasp was thus automatically determined. The fluctuating character of the

motor reaction determined the fumbling character of the response, and when a final powerful grip developed it was perpetuated by irregular fluctuations, such as could provide fresh sensory stimulation.

The instinctive grasp reaction therefore necessitates the existence of a mechanism which would appear to involve a highly discriminative sensory component to provide the perception and idea (so-to-speak) of something to be grasped. When it is also realized that the direction and adaptation of the response was often uncertain and erroneous and only successful after repeated fumblings its explanation can be reduced to two tropisms, neither of which is foreign to simple nervous mechanisms, and both of which are actively derived from the sensory qualities of the tactile stimulus. One so adjusts a movement that the stimulus reaches a maximal area, the other prolongs a reaction in the direction of the point of last contact. Thus movements of pursuit were in a direction radiating from the last point touched. The direction of movement of the contact itself was not of significance. It is of interest in this connection that sense of movement of touch in the normal human skin is very highly developed and has a very high degree of accuracy compared with ability to discriminate the direction of movement *along the skin surface* (Hall and Donaldson, 1885).

We found all stages of directional adjustment of the instinctive grasp, from a simple partial extension movement of the fingers in pursuit of a stimulus which was escaping from the palm, to an elaborate grasping in space (instinctive groping), sustained and directed only by a contact with some part of the hand every few seconds. We were satisfied that no part of this response need enter the awareness of the patient.

Instinctive grasping is therefore an integrated response to tactile stimulation of the hand with a high degree of adaptability and a property of projection into space. It could be entirely dissociated from conscious effort or motivation. Vision appears to add only a further projection in space and time to the basic response. The corresponding half-field of vision presented, so to say, the physiological counterpart of an extension of tactile surface. The eyes did not necessarily fix the object, though there was a tendency for them to do so and we felt that stronger distraction was necessary to maintain fixation of the eyes elsewhere during visual groping. We were never certain that we could initiate instinctive groping by a purely visual stimulus, i.e. without facilitation by a previous tactile reaction, though we have seen the affected hand rise to meet a moving stimulus more than a minute after the last grasp and while attention was directed elsewhere. We also obtained groping after a visual stimulus in the opposite visual half-field in one patient but there was also a slight

instinctive grasp response to be obtained from the opposite hand in this patient. It will be noted that we have not attempted to determine what modifications of the instinctive grasp reaction can be introduced by allowing the patient to give the affected hand his full attention and visual fixation. An elaborate system of control of ideation and motivation would then be necessary before valid conclusions could be drawn. We therefore cannot deny the contention of Walshe and Hunt (1936) that their first case exhibited volitional grasping, based on their observations that he preferred grasping a cigarette rather than a wisp of cotton, and that his anæsthetic hand grasped when he was allowed to watch the articles placed in it. In our own patients we did not find any evidence of discriminative factors in the instinctive grasp reaction, which occurred equally well with soft or hard, angular or smooth, spherical or tubular objects, provided a surface could provide sufficient initial contact to elicit a closing reaction, and was not nociceptive.

A fine delicacy of co-ordination and adjustment to highly specialized qualities of stimulus are found in true spinal reflexes such as the scratch reflex (Sherrington, 1906). In these respects the grasp reflex is comparable with such reflexes. But whereas the grasp reflex has a passive quality of matching its energy to that of the stimulus, the instinctive grasp reaction is an actively projected movement. The instinctive grasp response presents further features that take it out of the class of spinal or brain-stem reflexes, namely a projection of movement into the environment of the organism, and a quality of serial self-propagation of a succession, or chain, of responses each of which modifies the next so as to perfect the ultimate completion of the whole reaction.

Similarly the jaw opening reflex, followed by chewing or a sustained bite following stimulation of the alveolar margin near the teeth is readily obtained in the decerebrate preparation and was analysed by Sherrington (1917). The sucking reaction is projected to meet the stimulus and anticipated by vision. The analogies between the former and the grasp reflex, and the sucking reaction with instinctive grasping are completed by the common ipsilateral appearance of the corresponding pairs as a result of cerebral lesions, as in our Case 8.

The varying and confusing limitations which have been placed upon the word "reflex" have been fully discussed by Fearing (1930) and the term has been used by many in so wide a sense as to diminish its descriptive value. The type of distinction we wish to emphasize has, however, been encountered by others. From an extensive literature we select the lucid and authoritative account of Knight Dunlap (1922). In discussing the

differences between reflexes, instinct, and habit, Dunlap (1922) (pp. 210-213) speaks of inherent reactions whose "perceptual" and "ideational" qualities set them apart from the reflexes as "instinctive reactions". For example, "The instinctive auditory reaction includes among other details, the 'pricking up' of the ears." "There may be a few instinctive reactions, such as sucking, which are little modified, and persist for some time in practically the form of their first appearance" (p. 213). Their modification and association with other effects as a result of learning or conditioning result in "habits." An instinctive reaction differs from an instinct which is defined as "any combination of instinctive activities which produce a definite, and on the whole useful result" (Dunlap, p. 215). The classification of sucking as an instinctive reaction by Dunlap immediately brings to mind the essential unilaterality of that response, the associated movement of turning of the head, and its facilitation, or at times provocation, by a visual stimulus in the associated half-field. The frequency of appearance of instinctive sucking in association with grasping phenomena as a result of cerebral lesions has therefore a generic significance. The studies of Holmes (1930, 1938) on pathological visual fixation arising from frontal lobe lesions also indicates a disorder of the same general class. In this condition the image of a prominent object appears to determine movements of the eyes such as to fix the object and to follow it in any direction, and the patient could not move the eyes when requested. Only by momentarily abolishing vision of the object could the eyes be directed where desired. Labyrinthine nystagmus was obtained only in a dark room. Regarding the instinctive pecking response of newborn chicks, Lloyd Morgan (1926) has discussed the "clinging of gaze" that accompanies it and pointed its resemblance to the intense visual fixation of the human infant. The mechanism of visual fixation employs sensory data which Parsons (1927) classifies as highly discriminative ("epicritic") to secure a movement of which the end can, like instinctive grasping, be regarded as projected into the environment. Janischewsky (1909) described a patient with pseudobulbar and parkinsonian symptoms who presented the total syndrome of uninhibited instinctive visual fixation, and grasping ("reflexe saisseur").

We would point to the perceptual and ideational quality of tridimensional projection into the environment which the type of grasping with which we have been concerned shares with the instinctive auditory, visual and sucking reactions. We have therefore named it "the instinctive grasp reaction." We have further demonstrated in the case of the instinctive grasp reaction that the tropisms which give it the essential progressive and

projected quality can be reduced to terms of data derived from the adequate tactile stimulus and its localization.

Relationship of voluntary innervation.—Neither the grasp reflex nor the instinctive grasp reaction was found to be directly related to any disorder in the initiation or cessation of a willed movement of the hand. If the patient is able to co-operate in willed effort at all he can prevent or abolish the preliminary stages of instinctive grasping as he can a weak degree of the grasp reflex.

In both responses the difficulty in relaxation of the final stage of the reaction is probably related to inability to prevent renewed stimulation during traction on the grasping hand.

Willed extension of the fingers and wrist was universally used in the process of preventing further stimulation. As might have been predicted such extension was more effective in prevention than in release, for the initial conditioning reactions are brief and discontinuous. Full willed effort to extend the fingers may however have no effect in releasing the reaction in some patients so that the inability of the patient with paretic hand to release or prevent the grasp reflex is not necessarily related to his weakness in extension of the fingers. We did not, however, find any patient who was still able to prevent or release either type of response, lacking any power of extension of the fingers. The ability of some co-operative patients to cut short the holding phase of the grasp reflex without extension of the fingers, and the faculty of many to avoid both the grasp reflex and the instinctive grasp reaction, without finger extension, if their attention was not distracted, indicate the existence of power of direct suppression of both types of response.

We have no doubt as to the presence of both the grasp reflex and instinctive grasping in the newborn infant. Their reappearance in the adult as a result of cerebral damage indicates that the responses have been suppressed in the course of development, and not lost or converted into other reactions. They must in some manner enter into normal adult behaviour, but we have no evidence as to the part they play. In the patient who presents some ability to control the responses distraction of attention overcomes that ability. But attention as such is not the sole mechanism of control, for distraction of attention will not alone release the responses in many normal individuals. Nevertheless there are many "normals" in whom an unmistakable grasp reflex can be obtained when their attention is distracted and there are some whose hand will inevitably palpate and grasp a single object within reaching distance under the same circumstances. In such case neither type of response is as facile as in the patient with cerebral lesion.

The development of motor ability in the infant, as reported by Halverson (1936, 1937) indicates that his "closure" response, which we identify as a fragment of the instinctive grasp reaction, fades as "voluntary movement" (i.e. a psychologically motivated response) developed. Our findings indicate that further and more accurate information regarding the co-operation of visual fixation and the closure response in infants is necessary before "motivation" can be assumed to submerge the instinctive response. Schuster (1923) maintained that groping in the infant begins after the third to fourth month. The grasp reflex is obtainable for much longer in the infant than the "closure response," and our own observations indicate that it may never be completely lost. There is no indication that one type of response is evolved out of the other. Indeed there are strong objections to the consideration of instinctive grasping as an elaboration of the grasp reflex, for its quality of stimulus, its reflexogenous area, its complexity of movement and its lack of proprioceptive mechanism are of entirely different order. Each can occur independently. Each has perfect co-ordination of synergists and fixators. Thus the grasp reflex, the instinctive grasp reaction, and voluntary grasping represent three different levels of motor organization each independent of the other.

This independence of the grasp reflex and the instinctive grasp reaction appears difficult to account for except on the basis of separate and independent control of each by a cerebral mechanism which is so far unidentified. Our observations clearly indicate that the mechanism of appearance of the grasp reflex, the instinctive grasp reaction, weakness in willed movement, spasticity as well as rigidity is separate and independent for each disorder. We have purposely refrained from attempted identification of any of these disorders with localization of anatomical lesions, feeling that until some order is brought to the present confusion of ideas regarding motor function such correlation is of little value.

Tonic innervation as described by Wilson and Walshe (1914), with the closely related tonic foot response of Goldstein (1938), are occasionally seen in association with the grasp reflex and particularly when this occurs in parkinsonism. In our experience they represent a different category of disorder, which may provisionally be classed with dystonia, and which, in the hand, are more nearly related to the instability of posture called athetosis. The adequate stimulus for the grasp reflex and instinctive grasping as we have defined these can fail to elicit these responses. The tonic jaw response ("bulldog phenomenon") of Janischewsky (1928) appears to bear the same relationship to instinctive sucking that the grasp reflex does to instinctive grasping.

More directly associated with the circumstances of appearance of the instinctive grasping response and the grasp reflex is the peculiar postural aberration which is manifested by unstable rigidity. From the point of view of the clinician this phenomenon occurs as a variable resistance to passive movement, a "negativism" which has been described by Kleist (1927) and others as a counterfixation (*Gegenhalten*). It has been called the "psychomotor reaction of anticipation of passive movement" by Claude and his associates (1929). In the English literature it has been discussed by Bender and Schilder (1933). This phenomenon, with a commonly associated irregular tremor, is generalized in the musculature of the affected side, and with it belong the Mayer reflex and possibly a postural response in the arm that one of us (H. S.) will later report as the "bending reaction." Counterfixation, as well as the grasping responses, reflect the result of a loss of a system of higher motor integration which is separate from that which accounts for weakness in willed muscular contraction and spasticity. The subtlety of this defect is observable in the so-called "normal" arm of many hemiplegics. As the common result of a one-sided gross cerebral lesion which produces a crossed hemiplegia the arm of the same side as the lesion exhibits for a time mild counterfixation, a grasp reflex and sometimes instinctive grasping, and sucking may occur in the lips of that side.

Summary of Conclusions.

A clinical analysis of the involuntary grasping phenomena which appear as a result of cerebral lesions has led to their more precise definition and hence to methods of greater sensitivity in their elicitation. The *grasp reflex* has been defined as a stereotyped prehensile reaction of the flexors and the adductors of the fingers and the flexor muscles of the wrist which can be elicited in fractional parts by appropriate localization of the stimulus. The adequate stimulus for the full reaction is dual. The first essential is a distally moving deep pressure over a specific area of the palmar surface of joints in the hand, which elicits a rapid brief muscular contraction (the "catching" phase), which develops into a strong "holding" phase only if traction is made upon the tendons of the flexor or adductor muscles thus thrown into preliminary contraction. The response is then maintained only by traction. The chief difference between the holding phase and the myotatic resistance of spasticity is that the grasp reflex can be set up at any length of the finger flexors and is always self-sustaining.

The *instinctive grasp reaction* is a different type of response which is essentially a deliberate progressive closure of the whole hand made in a series of small movements, upon a stationary contact within the palm.

This movement terminates in a final complete grip. When well developed, or facilitated by repetition, the instinctive reaction will occur in response to stationary light tactile stimulation of any part of the hand. The closure of the fingers is then preceded by a more elaborate series of movements (the closing reaction) each of which brings further contacts with the stimulus and brings the stimulus closer to the palm. Removal of the stimulus will lead to movements of pursuit (magnet reaction) or to groping in space. Movement of the stimulus once confined within the palm leads to an immediate tightening of the grip (trap reaction). In both instances fluctuation of pressure of the contact is more important than movement along the surface of the skin. Location and total area of contact is the next most important factor and governs the intensity of the reaction. Stretch of tendons is not a factor in the stimulus. Groping in response to a visual stimulus is an extension of the tactile response and occurs when the instinctive grasp reaction is fully developed. Vision has no part in the remainder of the instinctive reaction.

The grasp reflex can be independent of both awareness of the patient and of power of willed movement. All manifestations of the instinctive grasp reaction except elaborate groping can also be found in states of semi-coma when psychologically determined responses are no longer elicitable. The basic features of both types of response are considered to be developed in fœtal and early infantile life and each is independent of the other. The grasp reflex should be classed with highly co-ordinated reflexes comparable with, but not belonging to, the righting reflexes. The instinctive grasp reaction presents a feature of projection in space which brings it into the category of the instinctive sucking reaction, and instinctive visual fixation reaction. The grasp reflex, and some fragmentary evidence of the instinctive grasp reaction, as we have defined these, was also found in the foot on the same side as the affected hand. The chewing reflex and the tonic jaw response bear the same relationship to instinctive sucking as does the grasp reflex to instinctive grasping, and appear unilaterally in common association.

The pathological features of both reactions is inability completely to suppress the first phase. A true grasp reflex with high threshold even when the adequate stimulus is applied can be obtained in many normal persons, and when once elicited can be as powerful as a pathological reaction. Both types of response are independent of the phenomena of spasticity and rigidity, and are separable from the effects of weakness in willed movement. They are more closely related to, but independent of, the fluctuating postural aberrations released by certain frontal lobe lesions.

The mechanism of their natural suppression, and hence of the reappearance of these infantile responses as a result of cerebral lesions, is related to unknown factors in the dominance of instinctive motor behaviour by part of the mechanism of awareness and motivation.

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LEGENDS FOR PLATES.

FIG. 3.—Electromyographic tracings of the grasp reflex. In this and the following tracings, time intervals are shown by the notches of a marker at the top of each tracing (two of which are indicated by arrows), recording 1 second intervals. The galvanometer tracings (E_1 and E_2) are accompanied by three narrower black lines which are a base line (lowest), a myograph record of muscular contraction of the long flexors of the fingers (F), and uppermost a tracing of the pressure exerted by the stimulus (S). 3A: In Fig. 3A the upper electromyogram (E_1) is from m. flexor sublimis digitorum, the lower (E_2) from m. flexor profundus digitorum of the right hand of Case 3. A grasp reflex was elicited by a stroke of the observer's fingers, beginning in the palm at CU, which met and pulled on the patient's flexing fingers at P. The observer's fingers overcame the grasp reflex at R, but stimulated a final burst at AD as they escaped over the terminal phalanges. 3B: From Case 6, right hand. Grasp reflex. The upper electromyogram is from m. flexor sublimis and the lower EMG from m. extensor communis digitorum. The sequence of events is as in fig. 3A. 3C: Grasp reflex from Case 3, right hand, as fig. 3A, except that the simple EMG is from m. flexor profundus digitorum. 3D: Case 3, five seconds after fig. 3C to show the effect of a more rapid distally moving firm pressure made over the first interphalangeal joints, which stimulated a more rapid and clonic grasp reflex. 3E: Case 2 left hand to show the discharge caused by a distally moving cutaneous contact alone at CU, provoking a catching phase alone. EMG from m. flex. profundus digitorum. For precise time intervals see time recorded in fig. 4A. 3F: Case 2, as fig. 3E, but showing the maximal effect of a rapid firm pressure (shown by the upper line) over the interphalangeal joints in a *proximal* direction at CU. The same pressure in a distal direction elicited a grasp reflex (fig. 4A).

FIG. 4A.—Case 2, paretic left hand, to be compared with figs. 3E and 3F from the same patient to show the grasp reflex evoked by a distally moving firm pressure over the palmar aspect of the interphalangeal joint beginning at CU. The pull on the fingers of the patient began abruptly at P. 4B: As fig. 4A, same hand to show an attempt to elicit a finger-jerk with the patient's fingers passively flexed in the optimal posture. The upper tracing shows the tap on the fingers. 4C: Case 2, right, non-paretic arm, which showed a clonic grasp reflex. EMG from m. flexor profundus digitorum. The fingers were passively flexed over the observer's fingers. At T,T,T,T, taps on the observer's fingers elicited finger-jerks. From CU onwards the observer's fingers also stroked the palmar surface of the patient's fingers gently in a distal direction, evoking a weak grasp reflex.

FIG. 5A.—Case 3. Right hand. The upper EMG is from m. flexor sublimis digitorum, the lower EMG from m. flexor profundus digitorum. A grasp reflex is provoked slowly, beginning at CU. The response changed from one muscle to the other as the stimulus moved distally. Speed of record as in fig. 5C. 5B:

Case 2. Left, paretic, hand. The one EMG is from m. flexor profundus digitorum. A grasp reflex began at CU, and the recruitment of four motor units is seen to occur step by step indicated by arrows. 5C: Case 3. As in fig. 5A. A grasp reflex was elicited during some preliminary groping. The transfer of activity from the superficial flexor muscle to the deep flexor is shown. 5D: Case 2. EMG from m. flexor profundus digitorum of right non-paretic arm during a grasp reflex, showing the typical fading of a partially clonic electromyographic pattern. 5E: From the same hand, to show a voluntary grip which underwent a slow relaxation beginning at R, in comparison with the grasp reflex (fig. 5D). Relaxation of willed movement was normally rapid but here a grasp reflex appeared to have been elicited during the voluntary movement. Compare with fig. 7A from the same patient.

FIG. 6.—A series of electromyograms from a patient with spastic quadriparesis from a cervical cord lesion. In each tracing the upper EMG (E_1) is from a deep flexor in the forearm (probably flexor profundus digitorum), the lower EMG (E_2) from the extensor muscles of the fingers. The latter shows irregular slow fluctuations due to electrode movement. Of the two tambour records the lower (F) records contraction of the flexor muscles. The upper (S) shows the passive resistance offered the examiner, from pressure in a balloon between the examiner's fingers and the patient's. 6A: Shows the effect of moderately rapid alternating passive extension and flexion of the patient's fingers. During passive extension (the rising upper tracing) a discharge was provoked in the flexors. The rate of stretch was a little more rapid in the second more clonic series. 6B: As in 6A except that a sudden passive extension is performed with distal movement against the palmar aspect of the patient's fingers in attempting to elicit a grasp reflex. 6C: Shows the effect of a sudden passive extension of the fingers with distally moving contact as to elicit a grasp reflex, during a slight initial voluntary flexion. The response is similar to that seen in fig. 6A with added voluntary contraction. 6D: Shows an attempt to elicit a grasp reflex while the patient was instructed to maintain slight flexion of the fingers. That the persistence of the response was due to purely voluntary contraction is shown by the abrupt cessation when the patient was told to relax at R.

FIG. 9.—Electromyographic records of instinctive grasping all from the right hand of Case 6. The upper EMG is from m. flexor sublimis digitorum, the lower EMG from m. extensor communis. The upper smoother mechanical tracing shows the pressure applied to the examiner's fingers, the lower more irregular line traces the contraction of the flexor muscles of the forearm. The observer's hand remained passive throughout. 9A: Shows the small bursts of discharge in the extensors during the small movements of adjustment to the shape of the stimulating object. 9B: Shows a grasping contraction as the observer's fingers entered the palm of the patient's hand, an initial broad contact having been made. 9C: Shows the effect of a simple contact with the palm. The adjusting movements developed into two gentle grasps. The second grasp later steadily developed into a powerful contraction which is not shown. It was similar to that in fig. 9D. 9D: Shows a firm grasp in progress, elicited only by contact, and at P the examiner sought to extract his stimulating fingers from the grasping hand (trap reaction).

FIG. 10.— From Case 8, right hand, to show in greater detail the relationship of stimulus pressure to the instinctive grasp reaction. In each record the upper EMG is from m. flexor profundus digitorum, the lower is from the main flexor group (? m. flexor sublimis digitorum). The irregular continuous line records the stimulus pressure passively applied to the palm of the hand by means of a button (about 4 mm. by 4 mm. surface) attached to a small balloon. The pressure

PLATE IX

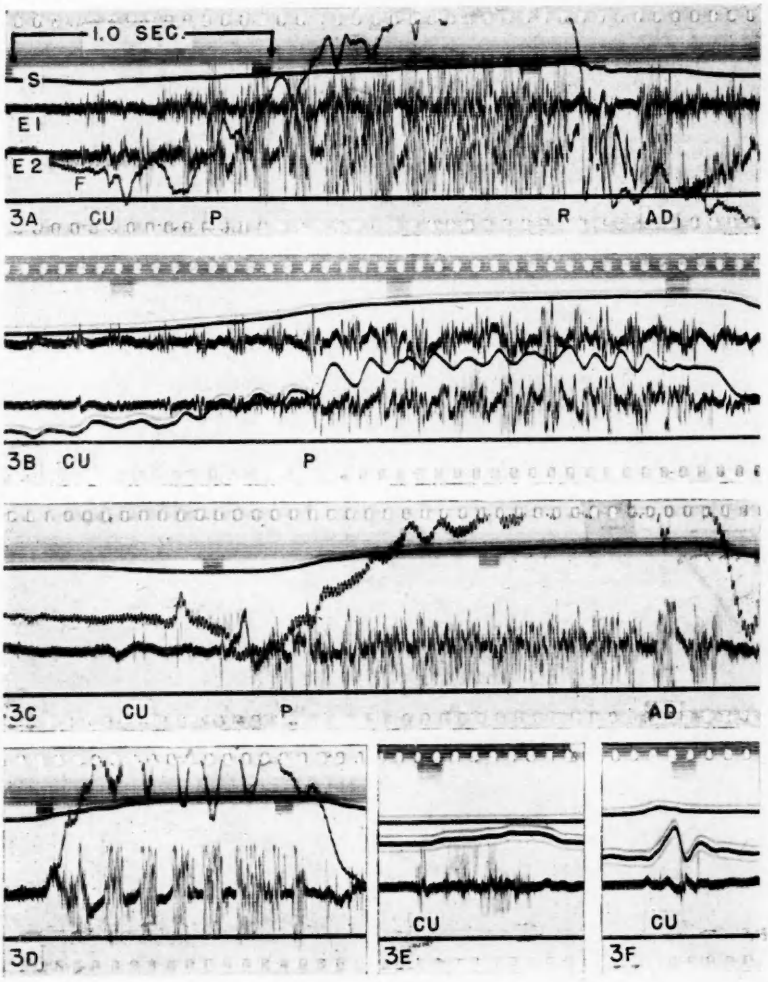

FIG. 3.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

PLATE X

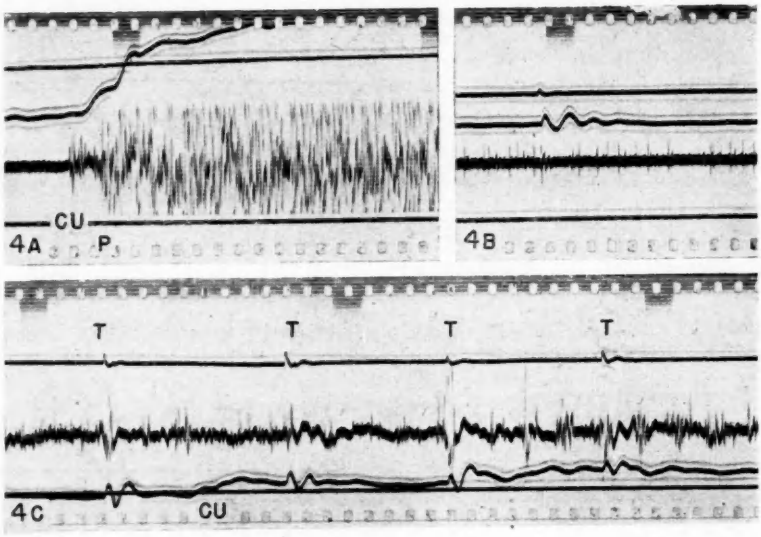

FIG. 4.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

PLATE XI

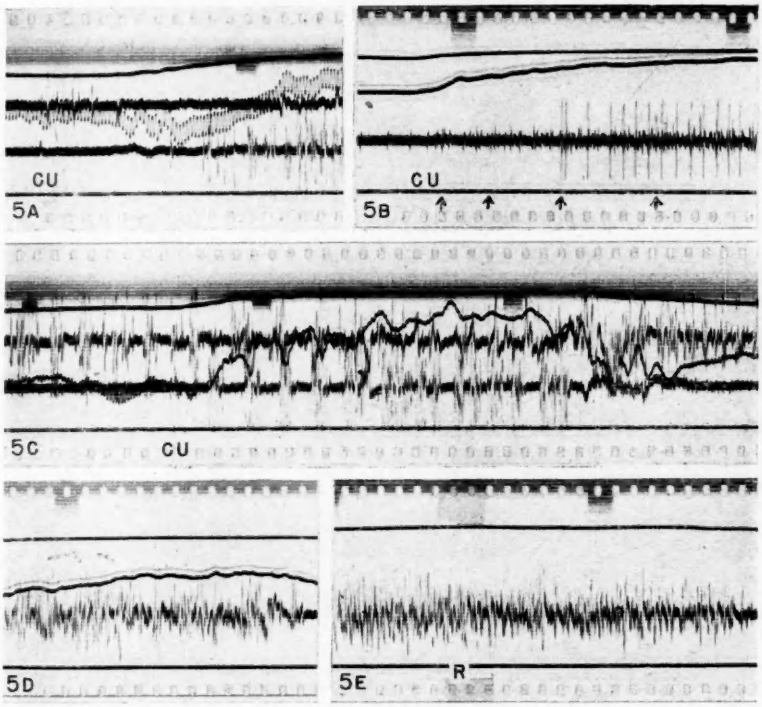

FIG. 5.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

PLATE XII

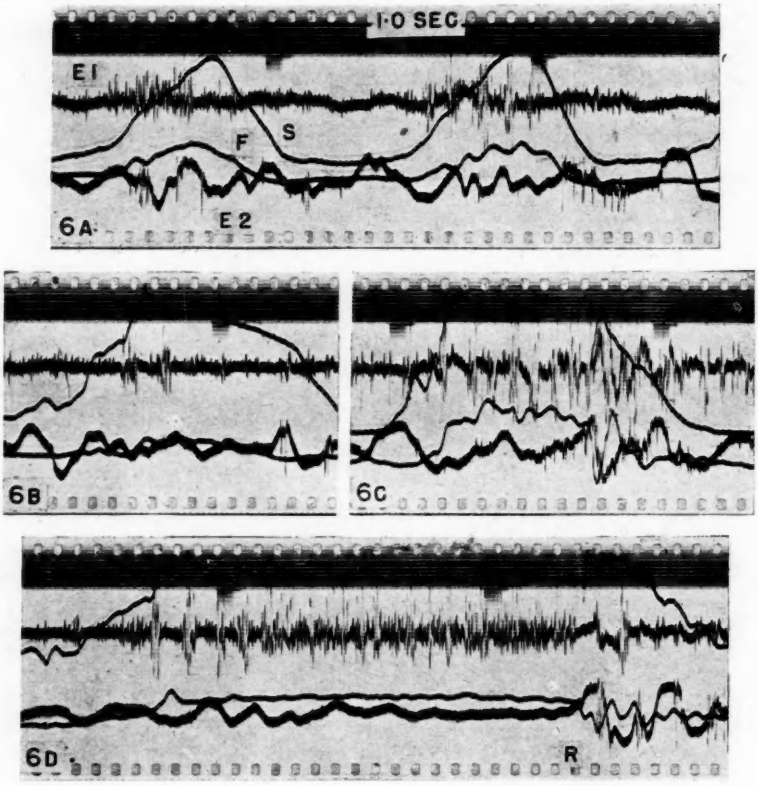

FIG. 6.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

1823

PLATE XIII

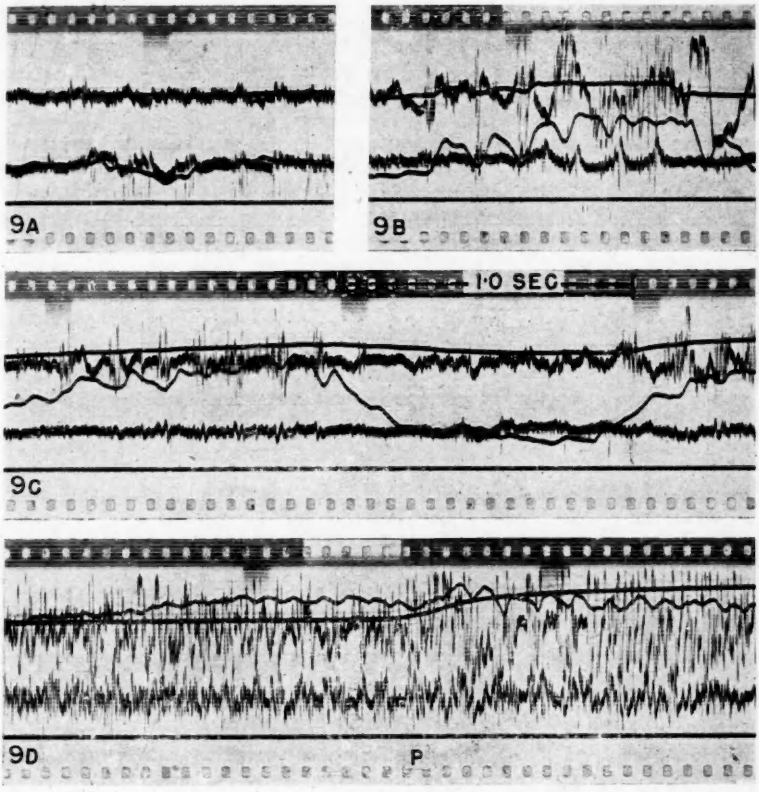

FIG. 9.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

PLATE XIV

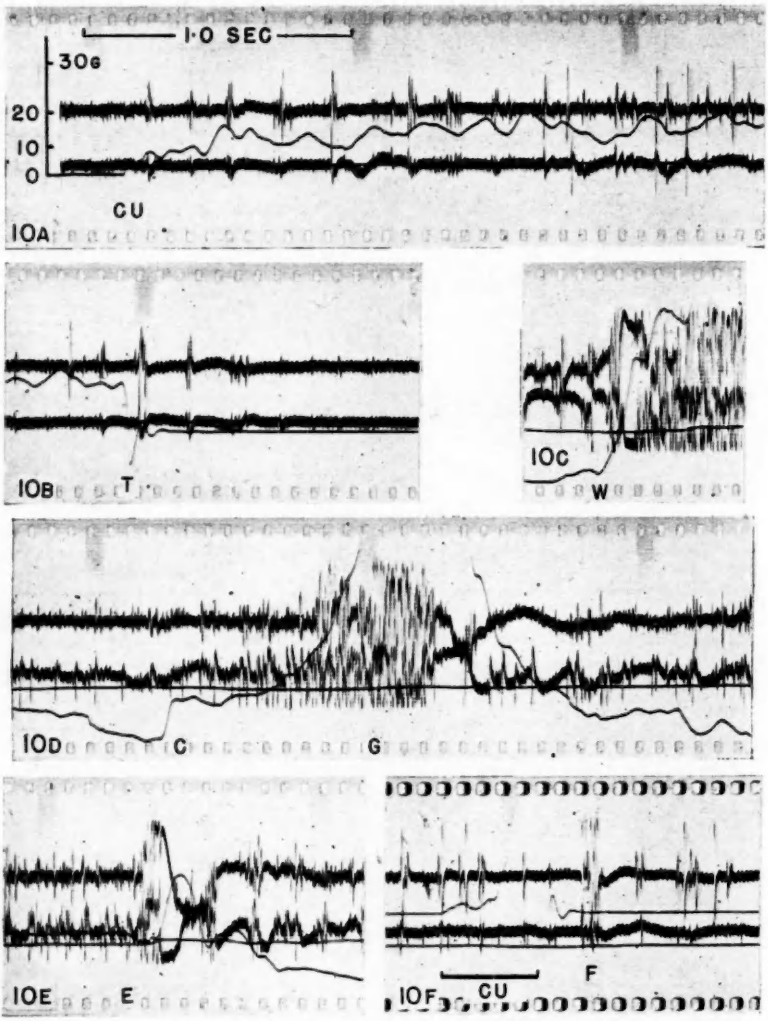

FIG. 10.

To illustrate article by Henrik Seyffarth and D. Denny-Brown.

in grams is shown on the scale to the left. 10A: The stimulus is applied to the radial side of the palm of the hand at CU and held as steadily as possible. A small clonic flexion movement began within 0·1 second (facilitated by earlier stimulation). Note the irregular fluctuations of stimulus contact pressure. 10B: The direct continuation of fig. 10A, to show the effect of sudden termination of the stimulus at T, before the closing fingers had reached the recording button. 10C: The stimulus recorder was enclosed within the hand and a slight movement of withdrawal at W elicited an immediate trap reaction which added further pressure to the recorder. The small lessening of pressure (over a broad area) at W stimulated the reaction. Zero pressure in this, and figs. 10D and E, is at the bottom of the tracing. 10D: The stimulus recorder is being subjected to palpation in the palm at the beginning of the record. At C a closing movement makes gradual transition into a mild squeeze or grasp at G. Variations in contact pressure are here entirely due to the grasping movements. 10E: The recorder was held in a light closing movement between the fingers. At E it is suddenly withdrawn and eventually escaped. The miniature trap reaction is followed by a movement of pursuit. 10F: A magnet reaction having been facilitated by a series of contacts, a fresh contact was made for the duration of the line CU. The lessening of action potentials during the contact probably corresponds to the brief extension of the fingers which was evoked.

REFERRED PAIN AND ASSOCIATED PHENOMENA.

BY

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I. INTRODUCTION.
II. REVIEW OF LITERATURE.
- A. Hypotheses Implicating the Spinal Cord.
- B. Hypotheses Implicating the Brain.
- C. Hypotheses Implicating the Peripheral Nerve Terminals.
- D. Summary of Literature.

III. OBSERVATIONS RELATING TO SOMATIC STRUCTURES.
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- B. The Reference of Pain.
- C. The Production of Cutaneous Hyperalgesia.
  - (1) Pain Threshold in the Hyperalgesic Skin.
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- D. The Production of Deep Tenderness.
- E. The Production of Muscular Spasm.
- F. Distinction Between Referred Pain and Referred Tenderness.
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- F. Somato-Visceral Reflexes.

V. SUMMARY AND CONCLUSIONS.
REFERENCES.

I. INTRODUCTION.

THE process by which pain is "referred" from one part of the body to another, and the cause of the various associated phenomena which customarily accompany this event (Ruch, 1947), are still imperfectly understood. Nevertheless, information regarding the general anatomical plan of the peripheral nervous system has been accumulating, and we believe that it is now justifiable to use this information to formulate a theory, capable of accounting for the reference of pain and concomitant disturbances. This theory depends essentially upon the existence of axon branching among the sensory pathways conveying the sensation of pain. It is the purpose of this paper to give an account of the development of

the theory, to consider its validity in the light of clinical evidence accumulated by other workers, and to evaluate its position in relation to the various theories now current.

II. Review of Literature.

A. *Hypotheses implicating the spinal cord.*—Sturge (1883) appears to have been the first to suggest that afferent impulses from the viscera, on arrival at a segment of the cord, are capable of setting up a "commotion" there, which may spread to affect other sensory afferents passing through the segment in question. This hypothesis was supported by Ross (1888), and was developed and amplified by Mackenzie, who postulated that an "increased stimulation" derived from a viscus might overflow from its normal channels and affect "neighbouring centres" in the spinal cord, so stimulating "sensory, motor and other nerves that issue from this part of the cord. Such stimulation of a sensory nerve will result in the production of pain referred to the peripheral distribution of the nerve, whose spinal centre is stimulated, so that visceral pain is really a viscero-sensory reflex. If the increased stimulus affects a motor centre, then a contraction of the skeletal muscle results, and thus is produced the viscero-motor reflex. . . ." This process renders the sensory centre in question abnormally sensitive, thus producing an "irritable focus." "Thus, the hyperalgesia of skin and muscle . . . is due to the fact that a stimulus, which would normally produce no painful sensation on reaching the spinal cord, excites an abnormally sensitive centre, with the result that the sensation of pain is felt" (Mackenzie, 1909).

This theory has been restated by Hinsey and Phillips (1940) in a way more in accordance with modern physiological terminology. These observers assume that "both somatic and visceral afferent fibres carry impulses which affect a common pool of secondary neurones, and that the principles of summation and inhibition are applicable." The suggestion that summation of visceral and peripheral impulses may be involved has also been made by Robertson and Katz (1938), Theobald (1941), Jones (1943) and Cohen (1947). Cohen further maintains that the results of nerve-blocking experiments necessitate the additional assumption that there is a constant stream of subliminal pain impulses passing to the central nervous system from terminals both in the viscera and in the periphery. This supposition is avoided by Ruch (1947), who accounts for most of the phenomena of referred pain on the basis of the convergence of visceral and cutaneous afferents on the same spinothalamic tract neurons, and considers that the only element of the referred pain syndrome

attributable to facilitation is hyperalgesia of dermatomal distribution. The scheme put forward by Ruch is shown in fig. 1.

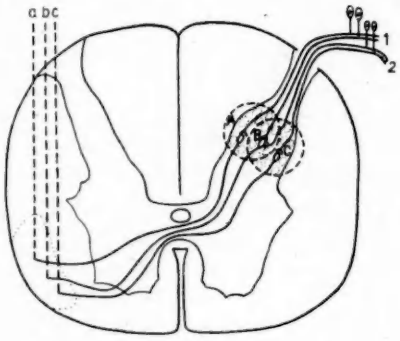

FIG. 1.—*Convergence-Projection Mechanism:* Convergence-projection mechanism of referred visceral and somatic pain based upon Sherrington's neuron-pool concept. A, B, C represent a neuron pool consisting of all the spinothalamic tract fibres originating in one segment of the spinal cord. A is the field of neurons having connections only with afferent fibres from cutaneous sense organs (1). B is the field of overlap constituted by neurons which receive impulses from *both* visceral (2) and cutaneous (1) afferents, and impulses in b will give rise to pain referred to the skin. c are those neurons of the pool which connect only with afferent fibres from the visceral cavities (2) and give rise to unreferred or true splanchnic pain. Only one neuron in each category is represented; others are indicated by "ghost cells." a, b, c, are fibres in the spinothalamic tract having cell bodies in fields A, B, and C respectively. (After Ruch, T. C., in Howell's Textbook of Physiology, 15th Ed., 1947.)

A number of difficulties, however, arise when theories implicating the spinal cord are used to explain some of the clinical findings. For example, if a process of summation is involved it is not easy to understand why in certain cases of referred pain anæsthetization of the pathway from the periphery produces no subjective effect (Woollard, Roberts and Carmichael, 1932; Livingston, 1938, and others). This difficulty is often met by a simple refusal to acknowledge the validity of the opposing evidence. On the other hand, the theory of Ruch (1947) does not account satisfactorily for the numerous cases where anæsthetization of the periphery completely abolishes referred pain (Weiss and Davis, 1928; Morley, 1931, and others).

As Lewis (1942) has pointed out, it is difficult, on the basis of our present knowledge, to explain why pain impulses from the *skin* do not more frequently give rise to referred pain if the cord disturbance theory is correct. Again, Mackenzie (1909) notes that it cannot be satisfactorily

explained why *pain* should be the only sensation resulting from a mechanism of this type.

Another type of objection arises from instances in which pain is referred to regions supplied by distant segments. Thus, Theobald (1941) reports the reference of pain from the territory of one cranial nerve to that of another, and Head (1894), Mackenzie (1909), Lewis (1942) and Wolff and Hardy (1947) note that pain of cardiac origin may be referred to the distribution of the 5th cranial nerve. Livingston (1943) finds that stimulation of the skin may on occasion give rise to pain in skin supplied by segments of the cord which are far distant from those supplying the area stimulated, and this phenomenon has been recently confirmed by Sinclair (1948). A possible explanation of these findings is to be found in the fact that "reflex collaterals from any given dorsal root ramify over a number of neighbouring segments" (Lloyd, 1944). Even if this is the true reason for the occurrence of "disturbances" in distant segments, it does not serve to explain all the problems of the distribution of referred pain, since it is still necessary to account for such observations as those of Head (1893, 1894).

In these classical papers, Head noted that visceral lesions do not always cause tenderness over the whole of their appropriate segmental areas. He states that in disturbances of the stomach, "instead of a whole tender area . . . we frequently find two tender spots from an inch to an inch and a half in diameter situated over the costal margin at about the tip of the 9th rib, together with a posterior spot generally situated near the 11th and 12th dorsal vertebræ, a little to one side of the middle line." He further emphasizes the fact that "every such area of cutaneous tenderness has one or more maximum points . . . to (which) . . . the patient refers his pain." Similar findings have been reported in connection with pain referred from the œsophagus (Weiss and Davis, 1928; Polland and Bloomfield, 1931), the digestive tract (Bloomfield and Polland, 1931; Jones, 1943), the genito-urinary tract (McLellan and Goodell, 1943), skeletal muscle (Kellgren, 1938; Travell and Bigelow, 1946), and pain caused by the stimulation of the central end of the divided phrenic nerve (Woollard, Roberts and Carmichael, 1932). Taken as a whole, this body of evidence on the exact manner in which pain is referred to the skin points to a specificity of response which necessitates the postulation of "definite fixed anatomical pathways" to mediate the phenomena (Travell and Bigelow, 1946).

B. *Hypotheses implicating the brain.*—Theobald (1941) rejects the view that referred pain is produced by a mechanism sited in the spinal cord, and considers that it is due to the "direct stimulation of cells in the

pain apperception centre of the brain." He assumes that in this centre the cells are "segmentally arranged and are intimately connected with each other and with different parts of the brain." He encounters difficulty in accounting for some of the reflex effects, such as muscular spasm, which accompany referred pain, and does not attempt to explain the results obtained by Lewis and Kellgren (1939) who found that, in the decapitated cat, the concomitant phenomena of referred pain, such as muscular spasm, could readily be produced. As previously noted, Cohen (1947) favours a theory involving the summation of visceral and peripheral impulses, but inclines to the view that such summation takes place in the brain rather than in the spinal cord. Lastly, Harman (1948) locates the essential mechanism for the reference of pain in the cortex, basing this conclusion on largely psychological grounds.

C. *Hypotheses implicating the peripheral nerve terminals.*—Many workers have suggested that in cases of referred pain there is a real peripheral effect. Penfield (1925) suggests that impulses arising from a viscus may produce referred pain by means of an axon reflex in the sympathetic system which leads to angiospasm or other changes in the periphery; these changes in turn produce pain impulses which thus have their origin in the area of reference. In this connection it is interesting that Travell, Berry and Bigelow (1944) have observed vaso-constriction of quite large vessels in the reference zone of pain produced by stimulation of skeletal muscle. Davis and Pollock (1932) and Pollock and Davis (1935) suggest that a metabolite is liberated in the periphery which in turn stimulates the sensory endings there, this process being mediated by efferent sympathetic fibres. In order to account for the spread of vascular phenomena following local injury of the skin, Lewis (1936) was led to conclude that a chemical substance was produced in the skin by the terminals of branched axon systems; and, later, Doupe (1943) suggested that this chemical is a metabolite formed by the activity of these nerve fibres. Lewis stated "The observations . . . definitely oppose the conclusion that stimulation of skin or of a cutaneous nerve leaves an impression on the central nervous system, such as may be referred subsequently as tenderness; they show that when such stimulation gives rise to distant tenderness, it does so, not through the central nervous system, but through a purely peripheral mechanism. Although this demonstration is immediately relevant only to the somatic nerves, it impresses the fact that the ideas of diffusion of impulses and of irritable foci in the cord resulting from visceral disease are purely hypothetical, and renders them less acceptable."

Morley (1937) suggested that "on stimulation of the phrenic nerve, efferent fibres in the posterior roots run down to the skin supplied by the 3rd, 4th and 5th cervical segments, and there liberate a chemical metabolite which stimulates the endings of adjacent pain fibres in the skin." He bases this theory on the work of Barron and Matthews (1934), who showed that many fibres in the posterior nerve roots could carry centrifugal impulses, and considered that many of these fibres started in peripheral sense organs and ran to the cord, where they gave off collaterals which left the cord again in either the same or in different posterior nerve roots. This interpretation has since proved difficult to sustain in the light of degeneration experiments, so that Barron (1940) has withdrawn his original contention, and believes that "at least two fibres may be involved."

Morley (1937), however, restricts the explanation quoted above to the case of shoulder tip pain, and indeed eventually postulates three different mechanisms to account for the reference of pain from the digestive system, the genito-urinary system and the diaphragm respectively.

Current theories implicating a peripheral mechanism nevertheless fail to explain satisfactorily the reference of pain to a completely anæsthetized area (Kellgren, 1938; Livingston, 1938; Brown, 1942, 1948) and many other clinical observations.

D. *Summary of literature.*—Stated broadly, then, the numerous shades of opinion can be reduced to two opposing beliefs. The first of these is that some mechanism located in the central nervous system is responsible for all the phenomena of referred pain, and the second is that these phenomena are produced by events taking place in the periphery. It is no doubt possible that by considerable amplication of one or other of these theories a hypothesis might be arrived at which would adequately overcome the objections which could be levelled against it. Nevertheless, the fact remains that, *as they are at present stated,* neither hypothesis is capable of explaining all the observed facts. Indeed, the proponents of either one of them appear to reject all or part of the experimental results in support of the other. However, opinion now appears to be so firmly set into two opposing camps that we feel that there would be no point in stating any new theory which does not profess to harmonize with the great majority of the experimental evidence. This evidence is of many and diverse kinds, but may be divided roughly into two main groups; one concerned with the reference of pain from somatic structures, and the other with the reference of pain from visceral structures. These two groups will be considered in turn, and since the theory to be propounded can be derived from a study of the "somatic" observations, these will be dealt with first.

III. Observations Relating to Somatic Structures.

A. *General considerations.*—Lewis (1938) appears to have been the first to point out that the pain resulting from the injection of irritant fluids into striated muscle is occasionally referred. Kellgren (1938) investigated this phenomenon in some detail by injecting hypertonic saline into various muscles and mapping out the areas of reference of the pain so produced; this work was subsequently repeated and extended by Inman and Saunders (1944). It was found that the areas so demarcated followed a roughly segmental pattern, though it was noted that this pattern did not correspond to the segmental pattern of the skin (cf. Sherrington, 1893). Later, Travell and Bigelow (1946) found, in similar experiments on skeletal muscle, that the pain involved several segments or portions of segments.

To study the segmental nature of the pain more easily, Kellgren (1939) made similar injections near the mid-line of the back, and succeeded in producing referred pain, cutaneous hyperalgesia and deep tenderness in areas remote from the site of injection. These areas were usually within the territory of the spinal nerve corresponding to the level at which the injection was made, but this was not always the case, and the occurrence of pain of "modified segmental" distribution was noted. This work was repeated and its implications in relation to the mechanism of referred pain were discussed by Lewis and Kellgren (1939). It was claimed that referred pain produced in this manner was the result of stimulation of the interspinous ligaments, and it was concluded that "Deep somatic and certain visceral structures are supplied by a common set of afferent nerves . . . this common system is responsible for all the pain and referred phenomena of visceral disease." In view of the far-reaching nature of these conclusions, curiously little effort has been expended in confirming the observations on which they rest, though Elliot (1944) used the method of saline injection to investigate the irritability of muscles in the area of reference, and Harman (1948) succeeded in provoking pain and paræsthesiæ in phantom limbs by this means.

Recently, however, Sinclair, Feindel, Weddell and Falconer (1948) have repeated some of the experiments reported by Lewis and Kellgren (1939), with the difference that the position of the injecting needle was controlled radiographically. They demonstrated that the technique described by Lewis and Kellgren is ill-adapted for the stimulation of the interspinous ligaments, but must unavoidably stimulate the sensory nerve trunks in the vicinity. Further, when adequate steps were taken to ensure that the injection was made into, or very close to, the interspinous ligaments,

a much larger volume of solution had to be injected in order to produce referred pain than when the injection was made in the region of the adjacent nerves. Indeed, in the lumbar region, where nerve trunks likely to be affected by the injection lie at some distance from the mid-line, it was frequently found impracticable to inject enough solution into the interspinous ligament to give rise to referred pain at all. This finding suggests that the results obtained may be attributed to the stimulation of nerve trunks, rather than of nerve endings in the interspinous ligaments or elsewhere, and this conclusion is supported by the further finding that pain of exactly the same distribution and character could be elicited from certain points in the paravertebral muscles by stimulation with a needle point. Exactly the same observation has previously been made, in relation to skeletal muscle elsewhere in the body, by Travell and Bigelow (1946), and it therefore appears that the occurrence of referred phenomena in response to the injection of an irritant fluid into deep somatic tissues is the result of stimulating nerve *trunks* running in these tissues.

B. *The reference of pain.*—It must be noted that to attribute the results simply to a stimulation in continuity of the nerve trunk supplying the area of reference would leave unexplained far more observations than it would account for. It is therefore necessary to inquire more deeply into the fate of the pain impulses set in train by the stimulation of a peripheral nerve trunk.

These impulses will traverse definite axonal pathways to reach some receiving centre in the central nervous system. Sherrington (1892) has demonstrated the occurrence of axon branching in the anterolateral ascending tracts of the spinal cord, and it is therefore possible that in some cases such axonal pain pathways may be joined by one or more others, not necessarily leading from the same area of the body. Barron and Matthews (1935) have emphasized that considerable integration of messages takes place in the spinal cord, and that what passes up the fibres of the spinal cord "is far from being a simple sensory discharge from peripheral receptors."

Such "integration" may also take place before the spinal cord is reached. Adrian, Cattell and Hoagland (1931) have shown electrophysiologically that in the frog axon branching may take place in the spinal nerves in such a manner that occasional pairs of fibres, one in the posterior and the other in the anterior primary division, may be derived from the same parent axon. Bifurcation of this kind was observed histologically in the frog by Hardesty (1905), and is pictured by Dogiel (1896) as occurring in mammals. In view of the frequency with which axon branching is found, both within the

central nervous system and in the peripheral nerves of mammals, the supposition that this particular arrangement might also occur in man is not an unfounded one. In this case, therefore, impulses arising in the territory of the posterior division and impulses arising in the territory of the anterior division must occasionally find themselves in joint possession of a single "final" pathway to the pain-receiving "centre." It has now but to be assumed that the "centre" is incapable of distinguishing the ultimate source of the impulses reaching it by these common pathways, and it becomes possible to explain how the stimulation of one branch of such an axon might give rise to the sensation of referred pain in the district served by the other branch. This mechanism is indicated diagrammatically in fig. 2.

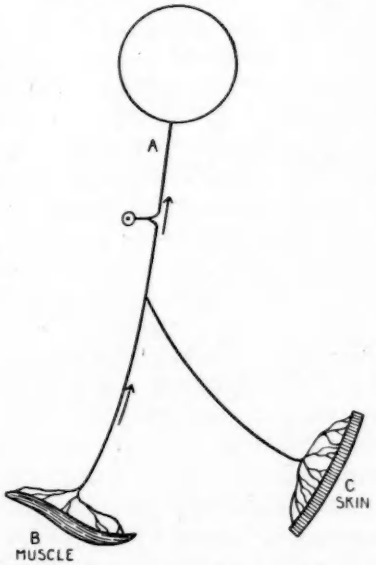

FIG. 2.—*Central Misinterpretation Mechanism:* Impulses passing up the common stem A of the branched axon from the muscle B are interpreted by the receiving centre as coming from the area of skin C.

If, then, it is assumed that axon branching may take place in man in such a way that the daughter axons pass into different branches of a nerve trunk, then it must be remembered that Hardesty (1905) and Adrian, Cattell and Hoagland (1931) have shown that the number of axons bifurcating in this particular way in the spinal nerves of the frog is small. It may

also be assumed that they are equally infrequent in the peripheral nerves of man. This assumption carries with it several implications.

In the first place, it could explain why stimulation of the terminal fine branches of a nerve is only rarely effective in giving rise to referred pain. In the skin, where such terminals form a dense network (Weddell, 1945), the number of terminals derived from branched axons must be relatively large in any unit area. Yet the production of referred pain by the stimulation of the skin is an unusual, though not unknown, event (Sherrington, 1900; Livingston, 1942; Sinclair, 1948). It has been found by Feindel, Weddell and Sinclair (1948), that in representative deep somatic tissues the pattern of innervation is characteristically less dense than that of the skin, and it therefore follows that in the deep tissues branched axons of this kind are necessarily even scarcer than in the skin. In the lumbar region of the back, it is possible to inject comparatively large quantities of hypertonic saline into the deep tissues near the mid-line without producing referred pain, though the local discomfort may be severe (Sinclair *et al.*, 1948). If, however, the saline is injected in the region of a nerve trunk of appreciable dimensions, referred pain may result. Now such a nerve trunk must contain all the axons the terminals of which are to be found in the area which it serves, among them being the small percentage of axons which possess sister branches elsewhere. Any stimulus adequate to affect the whole of the nerve trunk will therefore necessarily involve these axons, and so produce the phenomenon of pain reference. It also follows that the larger the nerve trunk stimulated, the greater the chance that it will contain at least one such bifurcated axon, and the greater the possibility that such stimulation will give rise to referred pain.

Secondly, since only a proportion of the axons have this dual connection, it may be assumed that their sister branches are scattered at random within the territory in which the referred pain is felt. This would imply that the endings to which pain is referred would in all probability be isolated from those of their neighbours also involved in the process. Since the localization of painful stimuli appears to be related to the multiple innervation of cutaneous pain "spots," as manifested by the overlapping and interweaving of adjacent pain nerve nets (Weddell, 1945), it is likely that the imperfect localization characteristic of referred pain (Mackenzie, 1909) can be attributed to the isolation of the peripheral terminals of the branched axon systems. This isolation could also explain the unpleasant character of pain referred in this manner. Weddell, Sinclair and Feindel (1948) have recently brought forward evidence, derived from the histological study of painful scars and areas of skin undergoing

reinnervation, to show that the occurrence of pain of unpleasant quality in response to stimulation of such areas is associated with isolation of the networks of fine beaded nerve fibres concerned in the perception of pain. The unpleasant quality and vague localization of pain aroused from deep somatic tissues has also been explained on this basis by Feindel, Weddell and Sinclair (1948), who found that isolated networks of fine non-myelinated fibres are a characteristic feature of the innervation of normal muscle, and are frequently to be found in fascia and periosteum.

C. *The production of cutaneous hyperalgesia.*—The occurrence of cutaneous hyperalgesia in the area of reference of pain aroused by the stimulation of somatic structures is a common and characteristic event (Lewis and Kellgren, 1939). If pain is referred from the area supplied by one terminal of a branched axon system to that supplied by another by a mechanism such as has been outlined, then it is clear that any pain impulses actually originating at the second terminal will serve to increase the intensity of the pain experienced. But such a simple summation theory will not account for *all* the facts, perhaps the most significant objection to it being that the onset of cutaneous hyperalgesia produced in this way may be delayed until after the local pain produced has disappeared (Lewis and Kellgren, 1939). Further, it has been repeatedly confirmed that while pain in the distribution of the nerve may appear almost at once, the cutaneous tenderness always requires some minutes to develop, and does not reach its maximum until nearly a quarter of an hour after the infliction of the local damage (Sinclair *et al.*, 1948). A delay of this order in itself suggests forcibly some chemical process, and the work of Lewis (1936, 1942) renders it likely that the effect is due to the liberation of a metabolite in the region of the active nerve endings as a result of antidromic impulses passing down the cutaneous limbs of the branched axon systems. Fig. 3 indicates diagrammatically the process involved.

It is well known that stimulation of the peripheral end of a cut posterior nerve root gives rise to flushing throughout its territory, and Foerster (1933) has used this method to map out the dermatomes in man. He has also recorded that this procedure may lead to the appearance of burning pain in the skin; this pain is felt in the region of overlap by intact nerves (Foerster, 1925). It is also interesting that Weddell and Sinclair (1947) have shown that the occurrence of impulses in pain pathways following the removal of a constricting cuff on the arm is closely associated with the reactive hyperæmia, which is known to be occasioned by a chemical mechanism (Anrep *et al.*, 1944). There is thus nothing improbable in

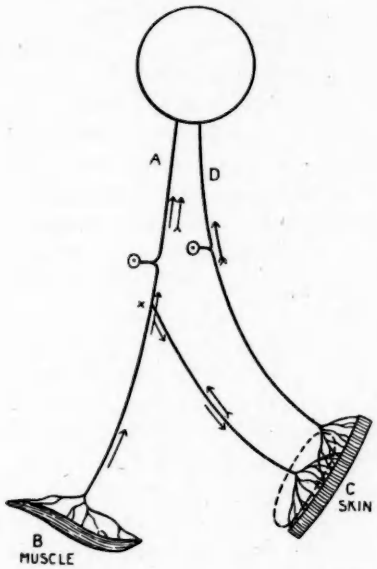

FIG. 3.—*Peripheral Chemical Mechanism:* Impulses originating in the muscle B pass antidromically to the skin C, where they give rise to a chemical disturbance (indicated by dotted outline) which causes impulses to pass up to the receiving centre via the branched axon A and also via its immediate neighbour D. Anæsthesia induced between the point of bifurcation X and the skin would affect this mechanism but not the central misinterpretation mechanism. (The arrows are flighted differently to indicate the different origins of the impulses they represent.)

associating the peripheral components of the pain reference syndrome with some chemical or metabolic factor, produced by antidromic impulses.

It might be argued that if this is the case it is perhaps surprising that the skin area does not invariably show signs of the hyperæmia which has occasionally been noted (Lewis, 1942; McAuliffe, Goodell and Wolff, 1943). There is, however, no evidence to show that the chemical factor concerned in the production of pain is identical with that giving rise to hyperæmia, and it therefore is not necessary to suppose that both phenomena must invariably be associated together. Moreover, it has been seen that the skin terminals of the branched axon system must be relatively few and far between. This implies that, while these terminals could readily produce enough chemical to affect some of their neighbours, it is unlikely that sufficient would always be produced to give rise to visible hyperæmia.

Wolff and Hardy (1947) consider that it is unlikely that chemical

agents are liberated into the skin in the production of the hyperalgesia, and quote experiments in which such hyperalgesia was produced by an adrenaline pack in the nose (Wolff, 1943). In these experiments the hyperalgesia disappeared almost immediately the stimulation was discontinued, and it is argued that therefore no chemical substance—at least no relatively stable substance such as was postulated by Lewis (1936)—can be responsible. There is, however, no need to postulate a stable chemical substance. Indeed, if a metabolite is responsible, then it is probable that it is vulnerable to rapid attack and destruction in the tissues. If this is so, then it must be only in special circumstances, such as almost continuous antidromic stimulation for long periods of time, that the production of the metabolite outstrips its destruction. It may then be assumed that the nerve endings, being thus exposed continuously to the action of an irritant, eventually become damaged, and thus respond abnormally to stimuli even though the production of the chemical has ceased, as in the experiments of Lewis (1936). The findings quoted by Wolff (1943) may thus be merely the result of removing the actuating stimulus before the stage at which damage to the nerve endings supervenes. In these circumstances the accumulated metabolite would very rapidly be removed by the normal mechanism of destruction, and the nerve endings, thus restored to their normal chemical environment, would almost immediately resume their normal function.

(1) *Pain threshold in the hyperalgesic skin:* In the skin, the presence of a number of endings exhibiting morphological abnormalities has been associated with a decrease in the pain threshold (Weddell, Sinclair and Feindel, 1948), and it seems possible that alterations in the physicochemical state of the endings might have a similar result (cf. Trotter and Davies, 1913; Trotter, 1926). Such alterations might therefore help to explain why areas of referred hyperalgesia, when tested by means of a nylon bristle or by a massive stimulus such as stroking with the hand, regularly give rise to a number of painful responses. That this pain also has a characteristically unpleasant quality (Lewis and Kellgren, 1939; Sinclair *et al.*, 1948) is probably to be explained by the additional fact that the individual endings affected are isolated from each other (Weddell, Sinclair and Feindel, 1948). Wolff and his collaborators, however, using a radiant heat stimulus have never been able to show that there is any significant lowering of the pain threshold in cases of hyperalgesia associated with deep pain (Wolff and Hardy, 1947). It may be that such a stimulus is incapable of demonstrating an alteration in threshold under these circumstances. For example, it is possible that at threshold intensity

a radiant heat stimulus acts by stimulating mainly the accessory pain fibres (Woollard, 1936; Clark, 1947) which run to the warmth receptors (Weddell, 1945), and possibly also by affecting the afferent fibres in connection with subcutaneous blood-vessels, and not primarily by direct stimulation of the naked pain fibres in the skin. It has already been seen that the total number of pain fibres involved in the process of reference must be small, and of these only a small proportion can be assumed to run as accessory fibres to warmth receptors. The chance of stimulating one of these must therefore be extremely small as compared to the chance of stimulating a free nerve ending by means of a needle prick. It is interesting, on the other hand, that Head (1893) notes that areas of skin tenderness referred from visceral disease may be hypersensitive to moderate warmth. Finally, Lewis (1942) observed that the behaviour of "erythralgic" skin was quite different from that of "hyperæsthetic" skin, in that the former readily gave rise to pain when exposed to heat, while the latter did not. In "erythralgia" it is probable that a large proportion of the nerve endings concerned are in an abnormal condition, whereas in the hyperæsthetic state, as has been seen, only a small number may be assumed to be affected.

(2) *The rôle of the nocifensor system:* Lewis and Kellgren (1939) maintained that the cutaneous hyperalgesia following on the injection of hypertonic saline into the back was identical in nature with that arising as a result of the stimulation of other areas of skin, and they therefore suggested that both conditions are provoked through axon or cord reflexes mediated by the hypothetical "nocifensor system" (Lewis, 1936). The existence of this system as a separate entity has been called in question, and Woollard, Weddell and Harpman (1940) claimed that "nocifensor" reactions travelled through the nerve apparatus subserving pain. Lewis and Kellgren (1939) rejected the supposition that the cutaneous hyperalgesia produced in their experiments was due to axon reflexes passing through the usual somatic pain nerves, because they maintained that "the pain nerves of the skin belong to a system separate from those running to deep-lying structures." They therefore found difficulty in supposing that the impulses could become transmitted from one system to the other, and concluded that they must travel, not in the pain nerves, but in the nocifensor system, which must, on this account, be assumed to be common to both superficial and deep structures. The grounds on which Lewis (1938, 1942) predicated the existence of two separate pain systems in the skin and in the deeper structures consist of differences in the quality of the sensation produced by painful stimulation of the skin and of the deep tissues, and differences in the reflexes which can be elicited from

these two sites. Recently, however, Feindel, Weddell and Sinclair (1948) have shown that the histological pattern of innervation in the deep tissues differs from that in the skin to an extent sufficient to explain satisfactorily the observed differences on which Lewis formulated his theory. It follows that the ordinary anatomical pain pathways are adequate to explain the reference of phenomena from the deep tissues to the skin, and it is unnecessary to call in the hypothetical nocifensor system to explain the observations.

D. *The production of deep tenderness.*—In addition to superficial hyperalgesia, injections of hypertonic saline near the nerve trunks in the region of the mid-line of the back give rise to referred deep tenderness (Kellgren, 1938, 1939). It is clear that this also is what would be expected to occur as a result of stimulating one branch of a bifurcated axon, since in many cases the other branch might terminate, not in the skin, but in muscle or other deep tissue. Lewis and Kellgren (1939), however, insist that the cutaneous hyperalgesia and the deep tenderness "are clearly different phenomena; their segmental areas do not correspond, and they develop and subside differently." In spite of this statement, the diagrams which they publish show a correspondence between the areas of deep and superficial tenderness which is surprisingly close considering the methods of testing which they appear to have adopted.

In any event, as was realized by Kellgren (1939) a given myotome does not necessarily occupy a position immediately internal to the corresponding dermatome. To take a conspicuous example, the area of skin known to be supplied by C5 differs widely from the area of skin covering the muscles supplied by this segment. The result of stimulating a segmental nerve is therefore not unnaturally to produce areas of deep and superficial tenderness which do not necessarily correspond (Brain, 1948).

The fact that the cutaneous hyperalgesia appears to last much longer than the deep tenderness (Lewis and Kellgren, 1939) is a difference in degree rather than in kind, and may perhaps be correlated with the pattern of innervation of the tissues concerned (Feindel, Weddell and Sinclair, 1948). Until more is known about the chemical and other factors concerned in the production of such hyperalgesia (Doupe, 1943), differences in temporal development cannot legitimately be used to imply that the mechanisms of the two conditions are entirely different (Lewis, 1942). It is therefore both simpler and more in accordance with the facts to regard deep and superficial tenderness under these circumstances as manifestations of the same general process.

E. *The production of muscular spasm.*—The occurrence of referred

muscle spasm in response to stimulation of deep somatic tissues was investigated by Lewis and Kellgren (1939), who noted that its distribution corresponded closely to that of the deep tenderness. It seems probable that this muscular "rigidity" which was shown in the cat to be independent of the presence of higher centres, is the direct consequence of the mechanism responsible for the deep tenderness. Just as in the skin the liberation of metabolites by antidromic impulses may set up an irritation of neighbouring sensory fibres, so in the muscle this process may cause impulses to be sent up to the spinal cord, where they give rise to a reflex motor response leading to contraction of the muscle and the appearance of spasm.

F. *Distinction between referred pain and referred tenderness.*—Lewis (1942) has pointed out that the concept of an "irritable focus" in the cord was introduced to account for the occurrence of referred tenderness and not for referred pain, and it is clearly desirable, as Lewis has suggested, to consider the two phenomena separately.

It has already been suggested that the reference of *pain* depends largely upon a central "misinterpretation" mechanism, whereas the occurrence of referred *tenderness* depends upon a peripheral chemical mechanism, both these mechanisms being mediated by branched axons. It has been postulated, however, that the peripheral chemical mechanism is also capable of giving rise to pain actually having its origin at the periphery, and that on occasions the misinterpretation mechanism can, by a simple process of summation, appear to produce hyperalgesia in the area of reference. In any given case it is legitimate to suppose that both of the mechanisms responsible for referring pain and both of the mechanisms for referring tenderness may be concerned, though it is probable that in the case of pain the misinterpretation process plays the greater part, and in the case of tenderness the reverse is true. In the light of this consideration such observations as those of Kellgren (1938) may be interpreted.

Kellgren (1938) produced pain referred to the hand by injecting hypertonic saline into the muscles of the forearm. He found that *tenderness* in the area of reference could be abolished if the skin and deep tissues were adequately infiltrated with local anæsthetic. This procedure did not, however, affect the referred *pain* felt in the area, which indeed continued undiminished even though the nerve trunk supplying the area of reference was blocked by local anæsthetic. In this case, therefore, the central "misinterpretation" component of the total effect—which would be unaffected by local anæsthesia or nerve block in the periphery—constituted by far the greater factor in the reference of *pain*, whereas the peripheral chemical

component, which was completely abolished by the anæsthesia, must have been concerned in the main with the production of local *tenderness*.

The importance of the misinterpretation mechanism in the reference of *pain* is also shown by the experiments of Harman (1948) who obtained pain referred to a phantom arm by injecting saline into the "interspinous ligaments," and by the observations made by Kunkle and Armistead (1947) on the spread of pain from fingers immersed in water to adjacent anæsthetized fingers. It is also worthy of note that Lewis (1942) makes the tentative suggestion that axon or cord reflexes might be concerned in the production of referred hyperalgesia, though not in that of referred pain, which he attributes to defective localization.

It is clear, however, that both the central and the peripheral mechanisms may have to be taken into account in dealing with either pain or tenderness. Thus, Inman and Saunders (1944) note that the referred pain produced by the injection of irritant solutions into deep somatic tissues tends to appear "at a varying interval of time after the infliction of the local lesion. This interval varies from a few minutes to a matter of hours." This observation may be interpreted as meaning that in these experiments the more obtrusive part of the total pain reference was due to the peripheral chemical mechanism, which requires time for its full development. Again, Morley (1937) reports the *immediate* development of hyperalgesia in the skin of the shoulders on stimulating the diaphragm. Morley further notices that when the diaphragm is stimulated with a swab and the area of reference in one shoulder is anæsthetized, there is less *pain* felt in the anæsthetized than in the normal shoulder.

This point will be further developed in connection with observations on the reference of pain from visceral structures, but it may be noted here that Robertson, Goodell and Wolff (1947), in a study of pain referred from the teeth, considered that pain cannot be eliminated *completely* until the afferent impulses from the primary source end spontaneously or are blocked.

Wolff and Hardy (1947) and Wolff and Wolf (1948), reviewing the evidence, consider two categories of referred pain, according to whether hyperalgesia is present or not. If it is present, they believe that the injection of procaine will abolish an element of the referred pain complex which is dependent on impulses (which ordinarily are non-noxious) from the zone of reference. These impulses produce pain on reaching the cord "in a segment involved in central spread of excitation." If hyperalgesia is not present, the pain depends only on the central effects of such a "spread of excitation" and therefore the injection of procaine in the area

of reference is without effect. They do not, however, suggest under what circumstances the two types of referred pain occur, nor do they explain the work of the supporters of the peripheral chemical theory (Penfield, 1925; Davis and Pollock, 1932, and others).

G. *The suggested hypothesis.*—So far, therefore, the consideration of the results of producing referred pain by stimulation of somatic structures has led to the formulation of the following hypothesis. The anatomical basis of the physiological processes concerned in the production of referred phenomena is the branched axon. In any given case there are two main mechanisms at work; the first of these is the misinterpretation by the central receiving apparatus of the source of the painful impulses, and the second is the production in the periphery, as a result of antidromic impulses, of metabolites which at first stimulate the nerve endings there and later damage them. It is probable that the operation of the first of these mechanisms gives rise chiefly to referred *pain,* while the chief result of the operation of the second is referred *tenderness,* but both mechanisms must be considered in relation to either phenomenon.

Anæsthetization of the area of reference will affect the second mechanism in two ways, first, by the interruption of the painful impulses arising there on their way to the central nervous system, and secondly, by the blocking of the antidromic impulses which are activating and perpetuating these painful impulses. The result of this procedure is therefore to abolish the pain and tenderness resulting from the operation of the peripheral chemical mechanism. Anæsthetization of the area of reference will not, however, affect the reference of *pain* by the first, or "misinterpretation" mechanism, though it will cut out the possibility of referred tenderness being produced by this mechanism.

In the early stages of the development of the reference syndrome the "misinterpretation" mechanism is predominant, since the chemical mechanism of necessity takes longer to become effective. In the later stages, however, the chemical factor may be the more important, and may be responsible for the persistence of hyperalgesia long after the removal of the original source of impulses. In brief, therefore, in the first stages of their development, pain and tenderness in the area of reference are, so to speak, an illusion, but rapidly become a reality, which may persist independently for some time after the original cause has been removed.

This theory, based upon experimental findings, is capable of explaining most of the published observations relating to the reference of pain and associated phenomena from somatic structures. It is perhaps premature to insist that the mechanisms suggested here are solely responsible for the

findings in every case of referred pain, and in particular it is undesirable to be dogmatic about such instances as the reference of pain to apparently unrelated segmental areas (Livingston, 1943). Further experimental work is necessary before such findings—which remain unexplained by any current theory—can be adequately discussed. Work along the lines described by Lloyd (1944) in relation to intersegmental pathways in the cord may well prove of importance in this respect.

It now remains to consider the experimental and clinical evidence regarding pain referred from visceral structures.

IV. Observations Relating to Visceral Structures.

A. *General considerations.*—Lewis and Kellgren (1939) clearly showed that they were able to reproduce the main features of the referred phenomena typical of visceral disease by stimulating somatic structures, and indeed were led to conclude that "there is no special form of pain, referred or otherwise, and no special viscero-sensory or viscero-motor reflex, which is the hall-mark of visceral disease." As has been previously stated, they explained their results by assuming that the viscera and the deep somatic structures were supplied by a common system of sensory nerves. It may be permissible to take this argument a stage further, and to postulate that branched axons exist, having one limb supplying a viscus and the other supplying skin or deep somatic tissue. The possibility of such a mechanism has already suggested itself to Fulton (1938) as a result of the work of Weiss and Davies (1928) which has already been referred to. Wernøe (1925) demonstrated the existence in fishes of branched axons with one terminal supplying the gut and the other the skin, and later he adduced evidence for the presence of a similar mechanism mediating the naso-ocular reflex in man (Wernøe, 1927). Further, there is no reason to stop at assuming a bifurcation, as there is nothing to prevent a single axon breaking up into a large number of branches, as it does, for example, in the skin (Weddell, 1945), or in skeletal muscle (Feindel, Sinclair and Weddell, 1947; Feindel, Weddell, Hinshaw and Sinclair, 1948). In this manner could be explained, not only the feasibility of impulses arising from the viscera being referred to somatic structures, but also the fact that such referred pain may sometimes be felt in the skin, or in the deeper structures, or in both.

Woodworth and Sherrington (1904) showed that "nociceptive" impulses in the splanchnic nerves pass up the lateral columns of the spinal cord and Hyndman and Wolkin (1943) conclude that ". . . the spinothalamic bundle of fibres is the physiologic unit through which is mediated the modality

of pain of whatever source." If the pain-conveying fibres from the viscera run in this manner, there is clearly ample opportunity for some of them to join up with axons derived from somatic structures (cf. Sherrington, 1892), thereby forming the necessary anatomical mechanism for the production of referred phenomena.

B. *The effect of anæsthetizing the area of reference.*—One of the shibboleths by which workers in this field are enabled to distinguish friend from foe is the effect produced, in cases of referred pain, by infiltrating the area of reference with a local anæsthetic agent. There is a considerable body of evidence to show that in many cases such local anæsthesia can abolish the pain or greatly relieve it (Lemaire, 1926; Weiss and Davis, 1928; Rudolf and Smith, 1930; Morley, 1931; Theobald, 1941; Jones, 1943 and others). However, other observers have been equally definite that no such effect occurs (Woollard, Roberts and Carmichael, 1932; Livingston, 1938; Lewis, 1942; Brown, 1942, 1948). In addition, many observers who reported favourable results record a number of incomplete or unsatisfactory cases for which no obvious explanation could be provided (Weiss and Davis, 1928; Jones, 1943 and others). Further instances are quoted by Wolff and Hardy (1947) who consider that the contradictions in the results "are more apparent than real." As has been discussed previously, however (Section III F), their explanation is not considered satisfactory.

It does not appear to have been observed that the unsuccessful results were recorded in acute experiments, such as stretching various organs by the inflation of balloons, stimulation of the phrenic nerve, &c. In these cases the stimulus was intermittent, and it may be assumed either that the peripheral mechanism resulting from antidromic stimulation had insufficient time to become established, or that such metabolites as were formed in the periphery were rapidly destroyed in the intervals during which stimulation was discontinued. In other words, the mechanism chiefly involved in the reference of pain in these cases was the central "misinterpretation" one, which would be unaffected by local anæsthesia in the periphery.

On the other hand, in the majority of cases in which local anæsthesia was successful in abolishing or greatly reducing the intensity of the pain, anæsthesia was induced some time after the onset of the pain—usually a period of the order of an hour or so. This time might well be sufficient for the peripheral mechanism, susceptible to local anæsthesia, to have become a major factor in the total effect, and, in cases where the original stimulus in the viscus had ceased to act, to be the cause of the whole of the pain. There are, however, a number of cases in which

success was obtained very shortly after the onset of the pain, and it is to be noted that in these cases the stimulus was a continuous one, allowing no intervals for recovery in the periphery.

There is, however, another factor which might serve to explain any residual discrepancies. It has already been said that in the case of pain referred from deep tissues, and therefore presumably also in the case of pain referred from viscera, many of the somatic terminals of the branched axon systems involved probably lie in the deep tissues. This arrangement is shown schematically in fig. 4. This may perhaps explain why anæsthesia

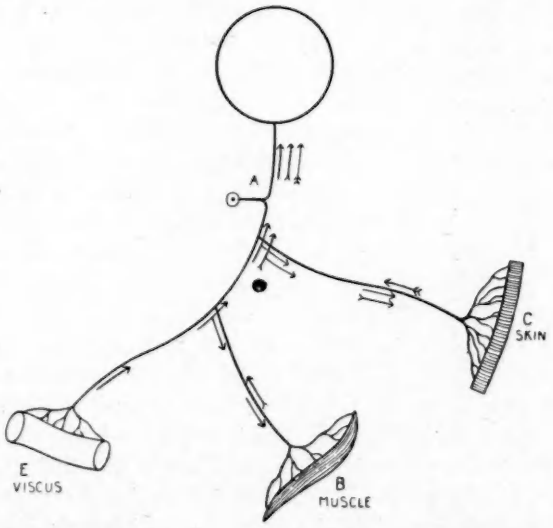

FIG. 4.—*Multiple Reference from a Viscus:* The arrows indicate the pathways traversed by the impulses set in train from a focus in the viscus E. Secondary pathways in unbranched axons have been omitted for the sake of clarity. (The different flighting of the arrows indicates the different origins of the impulses they represent.)

of the skin in some cases may cause the pain to change to a deep ache (Weiss and Davis, 1928; Rudolf and Smith, 1930; Jones, 1943). It may be assumed that in such cases the deep ache might be masked by the urgency of the impulses conveyed from the more richly innervated skin, and only revealed when these are removed by anæsthesia. Similarly the shift of pain so frequently described following anæsthesia of the area of reference (Rudolf and Smith, 1930; Jones, 1943; Cohen, 1947, and others) may be

explained in terms of the multiplicity of somatic terminals, often in different regions and at different depths, to which the pain may be referred.

Cohen (1944, 1947) objects to the hypothesis that a peripheral chemical mechanism is concerned on the basis of two cases (Cohen and Jones, 1943) in which pain was referred to a phantom arm by patients with cardiac disease. A similar case has recently been described by Harman (1948). It is argued, from the absence of any peripheral endings in these cases, that no such mechanism could operate. It is, however, perhaps significant that one of these men had a small neuroma, the anæsthetization of which abolished the arm component of the anginal pain when mild effort was undertaken (Cohen, 1947). Such a neuroma might well respond to chemical stimuli in much the same way as the peripheral terminals of a normal nerve. The further observation of Cohen and Jones (1943) that anæsthetization of the brachial plexus diminished the severity of the attacks can be explained as due to the blocking of impulses having origin in these neuromata as the result of antidromic stimulation. Since it has already been suggested that the majority of the referred pain in cases of this description is due to the action of the "misinterpretation" mechanism, it is noteworthy that only in mild attacks was such anæsthetization capable of abolishing the pain altogether.

C. *The effect of inducing hyperæsthesia in the area of reference.*—Cohen (1947) also notes the results of inducing hyperæsthesia in the area of reference by means of vesicant plasters, and states that referred pain of visceral origin can be produced or increased by such means. But if, as has been previously said, impulses from the viscera are interpreted as arising from the somatic terminal of the branched axon mechanism, which is in turn affected by a reflexly produced chemical stimulus, then any additional impulses having their origin at this terminal will serve to increase the intensity of the pain experienced. The application of vesicant plasters will not only provide such impulses, but will also tend to lower the threshold for painful impulses (cf. Schumacher, 1943; Hardy, Goodell and Wolff, 1941), so that stimuli such as the pressure of the clothing, which are normally unperceived, might swell the total number of pain-conveying impulses arriving centrally. It is interesting that Theobald (1941) has noted that the duration of hyperalgesia in cases of referred pain appears to depend on the degree of irritation to which the area of skin concerned is exposed.

D. *The effect of size of stimulus.*—Wolf and Wolff (1943) made observations on a patient with a gastric fistula, and showed that when the stimulus was limited in area pain was localized with indifferent

accuracy to the region of the stimulus; it was only when the stimulus involved the whole circumference of the stomach that referred pain was produced. This circumstance may well be explained by the probability that in the wall of the stomach there are only a few axons possessing sister somatic terminals, and that a large area has thus to be stimulated to ensure that at least one of these is affected. Downman, McSwiney and Vass (1948) have noted that the occurrence of reflex responses following stimulation of the intestinal wall may depend on the length of intestine affected by the stimulus. It is perhaps also relevant that Tower (1933) has found that in the frog a single afferent fibre covers a considerable area in the wall of the gut. The same sparsity of branched axons as has just been postulated may well be of importance in rendering the quality of the pain referred from a viscus unpleasant and vaguely localized (Weddell, Sinclair and Feindel, 1948; Feindel, Weddell and Sinclair, 1948)—as in such examples as the pain associated with ureteral calculi or angina pectoris. The same factor could also explain the numerous observations which have been made showing that the pain referred from viscera tends to be distributed in discrete, more or less circular, spots in the skin (Head, 1893, and others). These spots are explicable if it is assumed that they represent the areas innervated by the terminal branches of the somatic limbs of the branched axon systems supplying the viscera in question.

E. *Reference in stages.*—It is also interesting to consider the possibility that pain may be referred in a series of stages; for example, pain from a viscus might produce a chemical disturbance in a muscle, which, by affecting a second branched axon, might lead to the production of a similar disturbance in an area of skin; fig. 5 shows this occurrence diagrammatically. This type of phenomenon has been commented on by Wolff and Hardy (1947), who consider that the original focus gives rise to a "central spread of excitation" which leads to the appearance of muscle spasm. This spasm then acts as a secondary focus, and so on. As Theobald (1941), however, points out, if the central nervous system works in such a manner as to permit of the spread of "excitation" over the distances required by this theory, there would result a condition of chaos, both in the spinal cord and in the brain.

It may be noted, in passing, that a similar explanation may well apply to the results of anæsthetizing painful nodules in a skeletal muscle. Anæsthesia of most of these produces no more than a local result, but occasionally there is found a "trigger point" (Livingston, 1943), the anæsthetization of which leads to the abolition of pain and tenderness

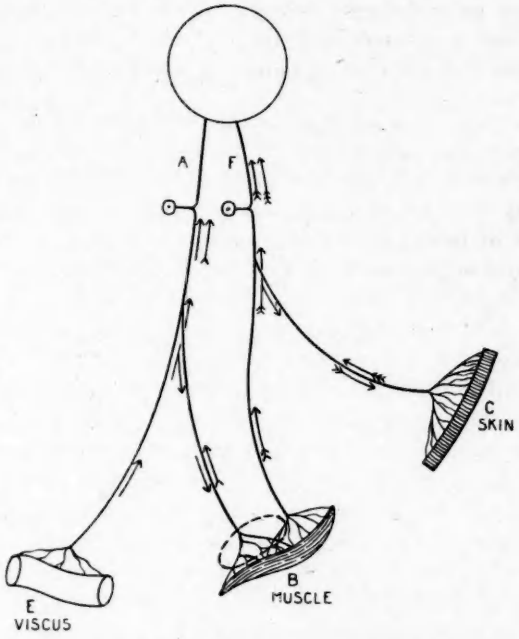

FIG. 5.—*Reference in Stages:* Impulses originating in the viscus E set up a chemical disturbance in the muscle B. This in turn initiates impulses which pass via the second branched axon F to the skin C. (The different flighting of the arrows indicates the different origins of the impulses they represent.)

throughout a wide area. It is quite possible that this "trigger point" represents the original source of impulses, which have set up secondary sources, each of which may have produced tertiary sources, and so on.

F. *Somato-visceral reflexes.*—A logical development of the whole argument of this paper is that each viscus has its own representation of somatic terminals in the skin, and a similar, though less dense, representation in the deeper tissues. If this is so, then it must be expected that impulses arising at the somatic terminals must find their way in an antidromic direction to the visceral terminals, and by there liberating a chemical substance, produce a series of effects in the viscus concerned. It is intended to develop this point in a subsequent communication, but it may perhaps be noted here that not only would such a mechanism be of the greatest importance in explaining many clinical phenomena, such as the initiation of anginal attacks by the

application of pressure to the left arm (Robertson and Katz, 1938), but it could afford a rational basis for the practice of applying heat or counter-irritants to the skin overlying an inflamed viscus (Sturge, 1883).

V. Summary and Conclusions.

A survey of the literature on the production of referred pain and its associated phenomena reveals that none of the existing theories is capable of explaining all the observations which have been made on the subject. In the light of recent work on the anatomical mechanisms underlying various aspects of pain sensibility in the periphery, and on the mode of production of referred pain from the deep somatic tissues of the back, a theory has been put forward which adequately harmonizes existing views.

It is postulated that an essential factor in the production of referred pain is the existence of branching among the sensory pathways conveying the sensation of pain. This branching is of such a type that one limb of a branched axon passes to the site of origin of the disturbance, and others pass to the sites to which the pain is referred. This mechanism works in two ways; first by leading to a misinterpretation by the central nervous system of the true origin of the pain impulses, and secondly by the liberation of metabolites at the terminals in the region where pain is experienced, thus giving rise to secondary pain impulses actually having origin at the periphery. In any given case, both mechanisms are concerned, the first being initially more important than the second, but the second increasing in importance with time, and in the later stages preponderating.

This theory rests on a basis of currently accepted anatomy and physiology, and is capable of explaining the numerous and sometimes divergent observations which have been made on the reference of pain from both somatic and visceral structures. It may well require extension and amplification particularly to account for the reference of pain and associated phenomena to distant segments. It is merely submitted that no theory which is put forward can afford to ignore the possibility that axon branching is responsible, at least in part, for the occurrence of referred pain and its associated phenomena.

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STUDIES ON COPPER METABOLISM IN DEMYELINATING DISEASES OF THE CENTRAL NERVOUS SYSTEM.

BY

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DEMYELINATING diseases of the nervous system in man represent a series of conditions the ætiology of which is at present obscure. Recent work, however, has thrown some light on the underlying cause of two demyelinating diseases of young lambs, enzootic ataxia, occurring in Western Australia, and swayback, occurring in this country and elsewhere. These conditions have been shown to be associated with a copper deficiency in the mother during pregnancy, and their development in lambs has been successfully prevented by copper therapy.

Although these diseases, occurring only in lambs and not in adult sheep, do not closely resemble demyelinating diseases in man, it was thought desirable to investigate the copper metabolism in disseminated sclerosis and related diseases, more particularly since four cases of neurological disease, clinically indistinguishable from disseminated sclerosis, have recently been reported among a group of seven scientific workers investigating swayback in this country (Campbell, Daniel, Porter, Russell, Smith and Innes, 1946).

Enzootic ataxia was first described in detail by Bennetts in 1932, and is apparently related to similar conditions in lambs described in other countries. In its acute form it affects lambs at birth, although more commonly it occurs subacutely as a slowly progressive ataxia in lambs 3 to 6 weeks old. The pathology of the acute form closely resembles that of swayback (Innes, 1939), and is characterized by a diffuse symmetrical cerebral demyelination most marked in the corpus callosum, internal capsules and the white matter of the occipital and frontal lobes, with additional degeneration of the motor pathways in the spinal cord. The lesions vary from microscopic changes to gross damage with liquefaction, porencephalic cyst formation and cavitation. Clinically, also, several of the cases described by Bennetts (1932, 1933) closely resembled the cases of swayback reported by Stewart (1932).

In the more commonly occurring subacute cases, cerebral lesions were rare, but degeneration of myelin sheaths in the cord, from the mid-dorsal to the mid-lumbar regions, was reported in 56 out of 57 cases examined microscopically (Bennetts and Beck, 1942); these lesions were most intense in the direct cerebellar and Lissauer's tracts. In both acute and subacute forms the characteristic lesion was a destruction of the myelin in the nervous system without damage to the grey matter.

Because of the confinement of the disease to certain "affected" pastures, and the absence of any evidence of an infective ætiology, Bennetts (1933) postulated the condition to be nutritional in origin. Initially plumbism was suspected, since it was known to produce encephalopathies in children, and has been reported as a cause of demyelination. "Deleading" experiments were therefore carried out with ammonium chloride which at first appeared to be successful (Bennetts, 1935). Further work in the following season, however, yielded inconsistent results, and showed that highly purified ammonium chloride was without effect, the earlier successful prophylaxis being due presumably to impurities in the commercial preparation used.

Spectrographic analyses of tissues for a number of elements showed that lead was present in the organs of "affected" and "unaffected" sheep in approximately the same proportions, but that copper was grossly deficient in the ash of livers of "affected" ewes and ataxic lambs (Bennetts and Chapman, 1937). In addition, these workers showed that the blood and milk copper levels of gestating ewes grazing on "affected" pastures were well below the normal figures. Examination of the pastures on which these animals were grazing revealed that these also were markedly deficient in copper (Bennetts and Beck, 1942).

Bennetts and Chapman (1937) investigated the effects of copper therapy, in the form of a daily drench of copper sulphate to pregnant ewes on the copper-deficient pastures. Their results showed complete prevention in the group to which copper was given, and 100 per cent incidence of ataxia in the progeny of the control group. They were also able to arrest the course of ataxia in lambs by the administration of copper.

In their final conclusions therefore Bennetts and Beck (1942) attribute enzootic ataxia in lambs to a state of copper deficiency in the gestating ewes, a condition which can be remedied by copper therapy.

In swayback, the relationship to copper deficiency is not as clear. Thus, the pastures of swayback areas are often apparently of normal copper content. Nevertheless, in their studies in N. Derbyshire, Innes and Shearer (1940) showed that the blood-copper levels of ewes grazing on "affected"

pastures were consistently much below the normal figure for these animals. Moreover, the blood-copper level could be raised to within normal limits by transferring the ewes early in pregnancy to pastures where the disease had not occurred (Eden, 1944; Shearer and McDougall, 1944). In addition the copper contents of the livers of "affected" ewes and swayback lambs were low, as was also the copper content of the ewes' milk (Innes and Shearer, 1940).

As with enzootic ataxia it was found that the administration of copper in the form of salt licks was able to prevent swayback (Dunlop and Wells, 1938; Dunlop, Innes, Shearer and Wells, 1939).

These studies provide ample evidence for an association between copper deficiency and the destruction of, or failure of normal formation of, myelin in the nervous system of the lamb. In view of this, the present investigation was undertaken in order to determine whether any evidence of copper deficiency or of abnormality of copper metabolism could be demonstrated in analogous diseases in man. The work has been mainly confined to disseminated sclerosis, since other forms of "spontaneous" demyelinating disease are rare, but a few cases of other chronic nervous diseases involving demyelination at some stage have also been studied. Owing to unforeseen circumstances it has not been possible to carry this work through to the stage of completeness originally envisaged, but in view of the interest attaching to copper metabolism in demyelinating conditions it has been thought advisable to report the work as far as it has progressed.

Experimental.

Material.—37 patients suffering from neurological disease have been studied; 28 of these were cases of demyelinating disease (26 disseminated sclerosis and 2 neuromyelitis optica), 4 presented with extrapyramidal lesions (3 Parkinsonian syndrome and 1 Wilson's disease), 3 were due to motor neurone disease, while the remaining 2 were diagnosed as radiculitis and spinal tumour respectively.

The patients with disseminated sclerosis could be divided into 23 cases of chronic disease (20 generalized form, 3 spinal type), and 3 cases presenting, at the time of investigation, acute retrobulbar neuritis (2 of these developed in addition other signs of C.N.S. involvement). The group of chronic cases was comprised of 11 of one to five years' duration, 6 of five to ten years' duration, 4 of ten to twenty years' duration, and two who had survived for twenty-five and twenty-eight years respectively from the onset of the disease.

Methods.—Copper estimations in blood, urine, liver and brain were carried out by modifications of the colorimetric method of Eden and Green (1940) based on reaction of the copper with sodium diethyldithiocarbamate.

To avoid contamination, the samples of liver and brain were taken directly into acid-cleaned digestion flasks, and the blood and urine into acid-cleaned bottles.

In most cases the material was digested with sulphuric, nitric and perchloric acids, although in a few instances the blood samples were dried at 100° C. and ashed at 300 to 400° C. for twenty-four to twenty-eight hours. The reagents used for the colour development were prepared with water freshly distilled over Pyrex or Hysil glass. Blank estimations were also performed on identical amounts of all the reagents used. The coloured compound was extracted either with carbon tetrachloride or isobutyl alcohol, and the final measurements of colour intensity made on a Hilger "Spekker" or Pulfrich absorptiometer.

A number of blood samples were also examined spectrographically. For this purpose, the blood was dried and ashed at 450° C. in an acid-washed silica dish. The ash was gently ground in an agate mortar, and approximately 0·01 g. portions were arced at 6 amps on 10 mm. pure graphite electrodes, with a slightly hollow cathode and blunt-pointed anode. The arc gap was 1 to 2 mm. The spectra were photographed on Ilford Long Range Spectrum plates after an exposure of 90 secs. The spectrograph used was a Hilger Medium Quartz pattern.

Results.

The effect of BAL on the urinary excretion of copper.—A start was made in the study of copper metabolism in the demyelinating conditions under investigation by comparing the levels of urinary excretion of copper in normal and diseased subjects. Urine was chosen rather than blood for the initial experiments since it was desired ultimately to study the effect of BAL on the excretion of copper, McCance and Widdowson (1946) and McDonald (1946) having shown that the derivative BAL-Intrav (Danielli, Danielli, Mitchell, Owen and Shaw, 1946) caused a marked increase in the urinary excretion of copper when injected into man or sheep.

2:3-dimercaptopropanol (British Anti-Lewisite or BAL) was introduced recently as an antidote to the arsenical vesicants (Peters, Stocken and Thompson, 1945). By virtue of the dithiol group in its molecule this compound reacts with arsenoxides to form relatively non-toxic compounds which are rapidly excreted from the body in the urine. It was soon

shown that BAL can also react with other metal compounds, including those of copper (Webb and van Heyningen, 1947; Thompson and Whittaker, 1947).

In view of McCance and Widdowson's findings in man, it seemed therefore as if BAL-Intrav might provide a useful tool for a study of the

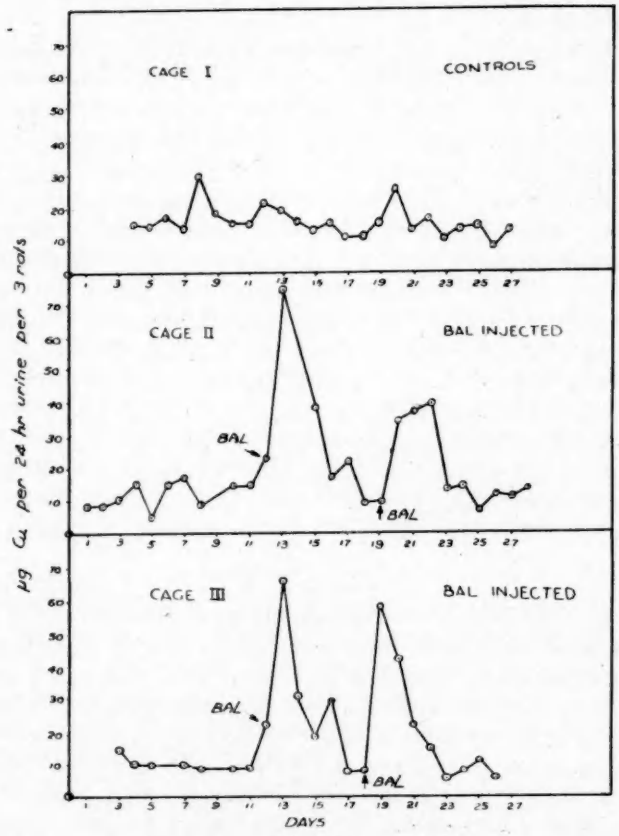

FIG. 1.

availability of copper in the body. Owing to the fact that BAL-Intrav is a relatively unstable compound which is not easily characterized or prepared in a suitable form for injection into man, it was decided to determine first whether BAL itself on injection into animals also causes increased

renal elimination of copper. Preliminary experiments (Stocken and Thompson, 1946) were therefore carried out with white rats.

Three metabolism cages were set up, each containing 3 rats. In order to prevent contamination of the urine with metals the metal mesh floor of each cage, together with any other metal parts of the cage with which the urine might come into contact, was coated with paraffin wax.

Twenty-four-hour specimens of urine were collected over a number of days, and the total copper excreted during each twenty-four-hour period determined. BAL, dissolved in propylene glycol, was then injected intramuscularly in doses of 75 mg./kg. body-weight into the hind-leg of each rat in two of the cages, the third cage being kept as a control. Immediately after injection the rats were returned to their cages and the collection of the twenty-four-hour specimens continued. Six days later the same rats were given a second injection of 75 mg./kg. and the urines collected for a further nine days.

No attempt was made to control the copper intake in the diet apart from giving the same diet to each cage throughout the experiment.

The results of these determinations are shown in fig. 1 from which it will be seen that the injection of this amount of BAL into white rats causes a very significant rise in the urinary excretion of copper. It should be pointed out that by comparison with the therapeutic dose of BAL for man the amounts of BAL injected were large; against this, however, must be set the fact that the estimations were made on twenty-four-hour specimens, and that any effect exerted by the BAL would be expected to last only a very few hours, so that if one- or two-hour specimens of urine were examined it might be anticipated that this effect on copper excretion would be exhibited after substantially smaller doses of BAL.

The procedure adopted with human subjects was therefore to collect two two-hour specimens of urine: 200 mg. BAL (= *circa* 3 mg./kg. body-weight) were then injected intramuscularly into the gluteal region, and two further two-hour specimens collected. 100 ml. of each specimen were then digested preparatory to the estimation of the copper, or, if the total volume was less than 100 ml., the whole specimen was taken.

Five normal subjects and eight cases of neurological disease were studied in this way; the results, given in Table I, are expressed as μg. Cu per two-hour urine flow.

It will be seen that in each case a very considerable increase in the output of copper occurred during the two hours immediately following the injection of BAL; in some cases this elevation persisted throughout the four hours studied. The increased excretion of copper was, however,

TABLE I.—EFFECT OF BAL ON URINARY EXCRETION OF COPPER
(μg. Cu/2-hour Urine).

Subject	*Sex*	*Diagnosis*	*Mean Cu/2 hrs. before BAL*	*Cu/2 hrs. 0-2 hrs.*	*after BAL 2-4 hrs.*
Ti	M	Normal	18·0	61·1	—
Ba	M	„	13·4	50·0	20·6
Ma	M	„	11·0	65·0	10·0
Ea	M	„	6·0	39·1	37·5
Tu	M	„	13·3	53·1	14·3
Os	M	Disseminated sclerosis	5·7	43·0	3·7
Sa	M	„ „	2·5	52·5	—
Ma	M	„ „	1·4	56·5	5·4
Sh	M	„ „	9·0	69·5	71·5
Ke	F	Parkinson's syndrome	14·0	43·7	—
Hi	M	Wilson's disease	41·7	109·0	43·0
Tu	M	Motor neurone disease	5·0	32·2	31·6
Co	M	Spinal cord tumour	17·3	43·9	37·7

just as marked in the patients with disseminated sclerosis as in the normal subjects. It is not known yet whether this increase represents merely a removal of circulating copper, or whether a true mobilization of copper from the tissues is involved, but it may be concluded from these experiments that under the influence of BAL, and under the conditions employed here, no evidence has been obtained of a lack of availability of copper in cases of disseminated sclerosis.

In view of the fact that in the small number of cases studied in these experiments the "resting" level of copper excretion appeared to be somewhat lower in the cases of disseminated sclerosis than in the control group, it was decided to compare the rates of copper excretion in larger groups.

TABLE II.—URINARY COPPER LEVELS.

NORMALS			DISSEMINATED SCLEROSIS		
Subject	*μg. Cu per 100 ml.*	*μg. Cu per 2 hrs.*	*Subject*	*μg. Cu per 100 ml.*	*μg. Cu per 2 hrs.*
Ma	10·5	11·0	Os	4·9	5·7
Ea	5·0	4·4	Ma	< 2	< 2
Fu	4·0	7·1	Sa	4·5	4·5
Tu	7·6	13·3	Ho	< 2	< 2
Ri	4·2	4·2	Pu	6·3	7·8
St	10·8	12·0	Sh	7·5	9·0
To	4·3	5·2	Bo	2·1	2·9
Gi	5·3	8·1	Jo	< 2	< 2
Ti	6·4	18·0	Re	11·0	3·0
Mean:	6·9 ± 0·9	9·7 ± 1·5			

OTHER CONDITIONS.

Subject	*Diagnosis*	*μg. Cu per 100 ml.*	*μg. Cu per 2 hrs.*
Br	Neuromyelitis optica	5·0	2·7
Hy	Retrobulbar neuritis	2·3	7·3
Wa	Parkinson's syndrome	6·0	17·3
Pl	,, ,,	3·0	8·5
Ke	,, ,,	6·5	14·0
Tu	Motor neurone disease	2·5	5·0
Go	,, ,, ,,	2·6	2·0
Da	,, ,, ,,	< 2	< 2

An attempt was made to collect twenty-four-hour specimens of urine for this purpose, but since difficulties were experienced in the satisfactory collection of specimens over as long a period under copper-free conditions, the final estimations were again carried out on two consecutive two-hour specimens. Table II summarizes the results obtained in 10 normal subjects and 17 cases of neurological disease, the mean of the two two-hour periods being expressed both as μg. Cu/100 ml. urine and as μg. Cu/2-hour urine flow.

As might be expected, very considerable variations were found in the copper levels of the urine samples, both in the normal and diseased groups. An even larger variation exists among the results already described in the literature. Thus, Rabinowitch (1933), comparing 50 different subjects found values ranging from traces up to 48 μg./100 ml. urine; Tompsett (1934*a*) found 8 to 48 μg./100 ml. in 16 normal subjects and van Ravesteyn (1944) a mean of 3·4 μg./100 ml. in four subjects (range, 1·4 to 6 μg./100 ml.).

In the limited number of cases studied in the present work, the urinary output of copper appears to be significantly lower ($P < 0·1$) in the patients with disseminated sclerosis than in the control group, 3 of the 9 diseased subjects having values lower than 2 μg. Cu./100 ml. of urine.

Blood copper level.—In view of the finding of low blood copper levels in ewes grazing on pastures where enzootic ataxia (Bennetts and Chapman, 1937) and swayback (Innes and Shearer, 1940) are prevalent, the blood copper level of patients with disseminated sclerosis was next compared with the level in a series of normal subjects.

Estimations were carried out on either 3 or 5 ml. samples of blood. In all, 19 normal subjects and 28 patients with neurological disease were examined. The results, expressed as μg. Cu/100 ml. blood, are given in Table III.

TABLE III.—BLOOD COPPER LEVELS (μg. Cu/100 ml. Blood).

NORMAL			DISSEMINATED SCLEROSIS		
Subject	*Sex*	*μg. Cu/100 ml.*	*Subject*	*Sex*	*μg. Cu/100 ml.*
Fr	M	145	Co	F	165
Mi	F	155	Mo	F	130
Le	M	190	Ad	F	125
Lo	M	170	Hi	F	105
St	F	145	Co	F	200
Ba-	M	105	Ha	F	190
Ca	M	120	Ph	F	180
Dr	M	120	Ne	F	350
Da	M	140	Br	M	200
El	F	135	Hu	F	220
He	F	135	Ir	M	170
Ke	M	135	Bo	M	200
Ma	M	120	Ke	F	200
Re	M	150	Re	F	215
To	M	225	Ba	M	125
Str	M	180	Sh	M	180
Wr	M	170	Wa	F	215
Ce	M	215	Ho	M	200
Man	M	100	Pu	M	120
			Tu	F	130
		Mean: 150 ± 7·9			*Mean:* 180 ± 12·1

OTHER CONDITIONS.

Subject	*Sex*	*Diagnosis*	*μg. Cu/100 ml.*
Br	M	Neuromyelitis optica	100
Hy	F	Acute retrobulbar neuritis	245
Ke	F	Parkinson's syndrome	160
Wa	M	„ „	155
Pl	M	„ „	210
Da	M	Motor neurone disease	145
Go	M	„ „ „	170
Bu	M	Radiculitis	100

The "normal" values for the blood copper level found by us ranged from 100 to 225 μg. Cu./100 ml. blood, with a mean value of 150 μg. ± 7·9. Although this mean level is slightly higher than some of the values reported recently in the literature (Holmberg, 1941; Sachs, Levine, Hill and Hughes, 1943), it is in good agreement with other results (Braun and Scheffer, 1940; Axtrup, 1943; van Ravesteyn, 1944), while somewhat below the mean values given by McFarlane (1932) and Tompsett (1934*b*).

No evidence was found of any significant lowering of the blood copper level in the cases of disseminated sclerosis, or in the other neurological conditions examined.

Hæmoglobin levels in disseminated sclerosis.—The rôle of copper in

the synthesis of hæmoglobin has been well recognized since the work of Hart, Steenbock, Elvehjem and Waddell (1928). Lewis (1931), Usher, McDermot and Lozinski (1935), Elvehjem (1935), Hutchinson (1938), Schultze (1940) and Poncher (1947), have all stressed the fact that copper is necessary for maximum hæmoglobin formation and erythropoiesis in animals and man.

If therefore a general deficiency of copper is playing a part in the ætiology of demyelinating diseases in man, it might be expected that patients suffering from these diseases might exhibit a moderate degree of anæmia, as shown by a fall in the hæmoglobin level. The hæmoglobin values and erythrocyte counts of the recent admissions to the Radcliffe Infirmary, Oxford, with disseminated sclerosis were therefore examined, and are given in Table IV.

TABLE IV.—HÆMOGLOBIN VALUES AND ERYTHROCYTE COUNTS IN DISSEMINATED SCLEROSIS.

Males *Name*	*Age*	*Hæmoglobin (Haldane method expressed as %)*	*R.B.C. Count ($\times 10^6/mm.^3$)*
Sh	44	88	—
Pe	39	124	—
To	33	101	5·46
Ha	42	118	5·75
Sa	30	112	5·26
Pr	38	110	—
She	43	118	—
In	30	110	5·24
Haw	41	104	5·32
Gr	59	84	4·10
Ro	46	94	4·70
	Mean:	106% ± 3·9%	
Females			
Bn	58	104	5·30
Yo	28	98	—
Hn	48	94	4·56
St	44	120	5·22
Ad	30	98	4·79
Ca	54	92	4·58
Co	30	84	4·10
Ha	37	106	5·50
Py	46	100	—
Tu	24	104	5·15
Ph	33	102	5·44
Hal	46	103	5·20
Mo	47	90	4·66
	Mean:	100% ± 0·5%	

It will be seen that the hæmoglobin percentage is well within the normal range for both male and female groups. Although this finding clearly does not, by itself, exclude the possibility of some local disturbance of copper metabolism inside the central nervous system, it at least provides no evidence of a general deficiency of copper in these conditions in man, such as is found in enzootic ataxia, where a co-existing anæmia is normally present.

Effect of repeated administration of BAL to rats.—Since injections of BAL give rise to the marked increase in the excretion of copper demonstrated above, it was decided to carry out some experiments to observe the effect of repeated administration of BAL to rats. If by this means the copper in the tissues can be mobilized and excreted from the body, it might, it seemed, be possible to produce an experimental copper deficiency. Although in the published work on experimental copper deficiencies in animals, produced by dietetic means (Hart, Steenbock, Elvehjem and Waddell, 1928; McHargue, Healy and Hill, 1928; Hart, Steenbock and Elvehjem, 1932; Schultze, Elvehjem and Hart, 1936; Potter, Elvehjem and Hart, 1938; Schultze, 1939), no mention is made of the development of any neurological signs in the animals concerned, it was thought desirable to determine whether a copper deficiency could be produced by repeated injections of BAL, and to observe whether, under these conditions, any neurological signs developed.

Three experiments were therefore carried out with this in view. In each case the BAL was dissolved in propylene glycol so that the amount to be injected was contained in a final volume of 0·1 ml. The injections were made intraperitoneally.

Although, as the experiments progressed, the general condition of the animals deteriorated, and the gain of weight as compared with control groups fell off, no neurological signs developed in any of the animals. In the first two experiments deaths occurred, after periods varying from forty-seven to fifty-seven days, and the remaining animals were killed off shortly afterwards. The amounts of BAL injected were as follows:

Expt. 1028. 6 white rats (31 to 38 g.).
40 mg./kg. daily (except Sundays) for twenty-eight days.
75 „ „ „ „ „ „ a further fourteen days.
113 „ „ „ „ „ „ the remainder of the experiment.

The first three deaths occurred forty-seven, fifty-one and fifty-four days respectively after the start of the injections, and the remaining animals were killed on the seventieth day.

Expt. 1064. 3 male white rats (118, 118 and 124 g.).
75 mg./kg. daily (except Sundays) for thirty-nine days.
90 „ „ „ „ „ „ a further twelve days.
100 „ „ „ „ „ „ the remainder of the experiment.

One animal died after fifty-seven days; the other 2 rats were killed after sixty-six days.

Expt. 1071. 12 female black and white rats (126 to 154 g.).
75 mg./kg. daily (except Sundays) for fourteen days.
90 „ „ „ „ „ „ the remainder of the experiment.

One animal was killed after twenty-seven days, and the remainder after thirty-six days.

TABLE V.—EFFECT OF REPEATED INJECTIONS OF BAL ON COPPER CONTENT OF BRAIN AND LIVER IN RATS. (μg. Cu/g. Tissue.)

Expts. 1028 and 1064.
White Rats. (Number of days of BAL injections given in brackets.)

Liver		*Brain*	
Normal	*BAL*	*Normal*	*BAL*
6·5	3·6 (51)	5·8	3·6 (47)
5·8	5·1 (54)	6·2	2·2 (54)
6·1	2·6 (57)	4·5	1·6 (57)
5·8	1·9 (66)	3·7	2·4 (66)
7·3	3·1 (66)	3·7	2·4 (66)
3·4	5·3 (70)	5·4	3·8 (70)
4·2		4·0	
4·5		3·1	
5·2		2·6	
5·4±0·4	3·6±0·6	4·3±0·4	2·7±0·4

Expt. 1071. 12 female black and white rats (126 to 154 g.).
Black and White Rats (First rat killed after twenty-seven days on BAL injections, the remainder after thirty-six days).

Liver		*Brain*	
Normal	*BAL*	*Normal*	*BAL*
5·2	3·4	3·5	6·4
5·0	3·1	2·3	3·0
6·7	3·3	3·1	3·1
6·4	2·2	3·3	3·1
7·3	3·5	3·2	2·1
6·4	3·1	3·6	2·2
	4·3		4·7
	3·5		2·9
	5·3		2·8
	3·3		3·5
	3·5		2·7
	3·4		2·3
6·2±0·4	3·5±0·2	3·2±0·2	3·4±0·4

Copper estimations were carried out on brain and liver, and compared with analyses done on tissue from normal rats. The whole brain was removed from the cranium with a bone spatula, and transferred after weighing into flasks for digestion with H_2SO_4 and HNO_3; the samples of liver were also removed with a bone spatula, and digested in a similar manner. The results of these estimations are shown in Table V.

The daily injections of BAL caused a significant decrease in the copper content of the liver; in the case of the brain the six analyses carried out in the first two experiments suggested that there is also some depletion in this organ if the BAL injections are carried on for fifty to seventy days. In Expt. 1071, on the other hand, no evidence was obtained of any lowering of copper content of the brain after thirty-six days; it must be remembered, of course, that the rats used in this experiment were of a different (black and white) strain. Although some doubt therefore exists as to the ability of BAL regularly to produce a decrease in the copper content of the brain it would appear that, under the conditions used here, repeated injections of BAL can cause a disappearance of copper from the liver.

Further indirect evidence of the production of a copper deficiency in these animals was obtained by the measurement of the hæmoglobin levels in both experimental and control groups in Expt. 1064, the results of which are shown in Table VI. Both groups of animals were fed the same diet, but the intake of food was not accurately determined.

TABLE VI.—EFFECT OF REPEATED INJECTIONS OF BAL IN HÆMOGLOBIN LEVELS IN RATS (HALDANE METHOD, EXPRESSED AS PER CENT).

	CONTROL				BAL-TREATED			
Date	*Rat* 1	2	3	*Mean*	*Rat* 1	2	3	*Mean*
22.4.47	88	78	80	82	86	—	82	84
2.5.47	100	86	70	85	88	106	82	92
23.5.47	100	92	96	96	80	80	84	81
6.6.47	102	96	102	100	84	84	84	84
25.6.47	110	—	—	(110)	86	—	—	(86)

From these figures it is evident that the rats receiving daily injections of BAL failed to show the gradual rise in hæmoglobin levels shown by the control animals. The degree of anæmia is not marked, but it is of interest that Hutchinson (1938), in his studies on anæmia of infancy, showed that on treating iron-deficient infants with pure iron the hæmoglobin levels rose from 34 to 77 per cent in three weeks, and reached 82 per cent after six weeks. Thereafter the figure remained stationary for several weeks till copper was administered, when the figure rose to 95 per cent within one week.

Until more is known of the detailed effects produced by repeated administration of BAL it is not possible definitely to relate this failure in the rise of the hæmoglobin values of the experimental rats specifically to a deficiency of copper, but, taken in conjunction with the demonstrated depletion of liver copper, it seems likely that the low hæmoglobin levels represent a sign of the overall copper depletion of the animals.

Copper content of human livers.—In view of the storage of copper by the liver which has been demonstrated in animal experiments (Golarewski, 1940; Clemedson and Norberg, 1945), and the lowering of the liver copper level which has been shown in enzootic ataxia, estimations of liver copper were carried out in normal human subjects and in patients with disseminated sclerosis. In the latter group the liver samples were obtained by biopsy, while the normal samples were taken at autopsy from accident cases. The results of these estimations are shown in Table VII.

TABLE VII.—LIVER COPPER LEVELS (μg. Cu/g. Wet Wt.) IN NORMAL SUBJECTS AND IN CASES OF DISSEMINATED SCLEROSIS.

Normal		*Disseminated sclerosis*	
Da	15	Ch	14
En	6	Ha	10
Gr	20	He	10
Ha	7	Ki	14
Hi	18		
Me	18		
Mean:	14	*Mean:*	12

In the 4 cases which have been studied no evidence of lowering of the liver copper level was observed in disseminated sclerosis, and as liver biopsy in these cases involved an abdominal incision it was not felt justifiable or necessary to proceed further.

DISCUSSION.

Although incomplete, the studies on disseminated sclerosis described above do not provide definite evidence of any abnormality of copper metabolism in this condition in man. No difference was detected between patients with disseminated sclerosis and normal subjects either in the blood copper level or in the urinary excretion of copper in response to injected BAL. It is true that the urinary copper level in the absence of injected BAL appears to be somewhat lower in the diseased than in the normal group. This difference, however, may well be an indirect outcome of the conditions of invalidism of the diseased group rather than a pre-existing sign of the cause of the condition.

Further, rats have been injected over relatively long periods with BAL, a drug shown to cause a marked increase in the urinary elimination of copper, and have failed to develop any neurological signs even though low hæmoglobin values were produced and, at autopsy, low copper contents of the livers were demonstrated.

Disseminated sclerosis, however, does not resemble swayback very closely despite its apparent occurrence amongst swayback-workers. It is a disease of early and middle adult life, and has not been reported in the newborn, whereas swayback appears to be ante-natal in origin. Even with a demonstrable copper deficiency and anæmia ewes grazing on "affected" pastures have shown no ataxia, nor have neurological signs been reported in diseases of other adult animals which have been attributed to a copper deficiency, and which have responded to copper therapy (Neal, Becker and Shealy, 1931; Thomas and Wheeler, 1932; Sjollema, 1933, 1938).

It would appear therefore that while copper may be essential for the normal development of the central nervous system, once the nerve-tracts have been laid down nervous function can proceed apparently normally in the presence of a demonstrable copper deficiency.

In view of the finding of Glazebrook (1945) who reported a high copper content in both the blood and liver in Wilson's disease, it is of interest to note that the one case of this condition studied in this series showed a much higher urinary excretion of copper than that observed in any other subject.

The above work was carried out as an extension of a research into the ætiology of disseminated sclerosis being conducted in the Departments of Neurology, Radcliffe Infirmary, Oxford, and Bristol University, under the direction of Dr. W. Ritchie Russell and Dr. A. M. G. Campbell respectively, to whom we would like to express our thanks for the cases placed at our disposal. We are also grateful to Professor R. Milnes-Walker for the liver biopsies, to Dr. R. B. Fisher for his assistance with the statistical interpretation of our results, to Mr. J. R. P. O'Brien for his interest in the work, to Dr. C. Whitty for his help with the clinical material, and to Miss D. Davies for her skilful technical assistance.

Summary.

(1) A study of copper metabolism in disseminated sclerosis and other chronic diseases of the nervous system has been undertaken.

(2) The increased urinary excretion of copper produced by an injection of BAL has been shown to be of the same order both in disseminated sclerosis and in normal subjects.

(3) The level of urinary copper shows wide variations, the cases of disseminated sclerosis showing a slightly lower excretion rate.

(4) No difference was detected in the blood copper level between normal subjects and disseminated sclerosis patients.

(5) Examination of case records showed that the hæmoglobin levels in disseminated sclerosis were within normal limits.

(6) Repeated injections of BAL into rats causes a lowering of the hæmoglobin level and also a depletion of liver copper. These copper-deficient animals, however, showed no neurological signs.

(7) It is concluded that the work described here does not provide any definite evidence of abnormality of copper metabolism in the conditions studied.

(8) The observations reported are to some extent incomplete, as circumstances have prevented the work being carried through to the stage originally envisaged.

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